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RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		A biomarker and pathway discovery program in autoimmune renal diseases
Name		Dr Prasanti Kotagiri
Award Received		2018 Jacquot Research Entry Scholarships in Nephrology
Report Date		December 2019
Administering Institution		University of Cambridge, UK
Funding Period	Start Date:	1/01/2019
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PROJECT SUMMARY

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a disease of the immune system. Treatment remains crude and relies on relatively non-specific and toxic treatments. AAV can have a very different clinical course between individuals which makes tailoring treatment very attractive.
What clinicians in this field therefore need is a way to accurately assess disease severity, pre-empt flares and predict long term outcomes. The latter should allow stratified therapy with more intensive medications being reserved for those with poor predicted outcomes, in whom their risks can be justified. In patients with a predicted good outcome, such therapy could be avoided, reducing toxic side-effects. Additional benefits of such a test would be the ability to predict disease relapse prior to the onset of overt clinical symptoms, allowing for prompt treatment and thus reducing the chance of irreversible damage to organs, such as the kidney.
Neutrophils, an immune cell, play an important role in the development of AAV. We hope to gain a better understanding of disease by analysing the gene expression of these cells and their relationship with disease subgroups, immediate disease activity and long-term outcome.

PROJECT AIMS / OBJECTIVES

AAV is a heterogenous condition with the spectrum of disease ranging from a rash, to pulmonary haemorrhages, to severe renal involvement resulting in end stage renal failure. The variability in presentation and outcome represents a significant challenge for clinicians caring for patients with the condition.
In this project, we wished to better understand AAV vasculitis, in particular, what determines disease manifestation, severity and outcome. To achieve this, we have integrated neutrophil transcriptomic data, generated in patient cohorts with vasculitis, with clinical data to discover novel prognostic biomarkers and associated pathways.

SIGNIFICANCE AND OUTCOMES

We uncovered a modular expression of interferon stimulated genes in MPO-AAV which was absent in PR3-AAV. The interferon signature was confirmed by its presence in SLE, a disease well known for its heightened expression. This signature was present during the time of active disease and at 3 months post treatment. The interferon signature was not able to differentiate the two antibodies subtypes at 12 months. The signature was present in the Neutrophil, Monocyte and PBMC transcriptome but was absent in T cells. Multi-omic factor analysis revealed upregulation of interferon associated proteins, coinciding with the increase in gene expression.

AAV causes severe morbidity and mortality. The differential expression of interferon in MPO compared with PR3-AAV highlights differences in pathogenesis. The presence of an interferon response in MPO-AAV opens new avenues for targeted treatment with agents such as Jak inhibitors and monoclonal anti-IFN-α antibodies.

PUBLICATIONS / PRESENTATIONS

Differential Expression of Interferon-Stimulated Genes in ANCA-Associated Vasculitis, American Society of Nephrology, Poster 2020

(https://www.asn-online.org/education/kidneyweek/2020/program-abstract.aspx?controlId=3449463)