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RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		Regulatory T Cells and HLA Associations in Autoimmune Renal Disease
Name		Dr Kate Robson
Award Received		2018 RACP Jacquot NHMRC Award for Excellence
Report Date		11/02/2022 – Year 3 Report
Administering Institution		Centre for Inflammatory Diseases, Monash University at Monash Health
Funding Period	Start Date:	01/02/2018
	Finish Date:	01/02/2021

PROJECT SUMMARY

Autoimmune diseases, involving the immune system attacking our own body, cause a significant burden of ill health. Most autoimmune conditions are linked to specific types of 'HLA' (human leukocyte antigen) proteins on the surface of cells. Reasons for these links are generally not well understood, but have recently been outlined in Goodpasture's disease, an autoimmune condition affecting the kidneys and lungs.

This project aims to use Goodpasture's disease as a model to examine the interactions between different HLA proteins and immune cells. Defining the structure and behaviour of these cells may help us understand why some individuals are more susceptible to, or protected from, autoimmune disease. These insights into immune system regulation could also be key to the development of more effective and more tolerable treatments for Goodpasture's disease and other autoimmune conditions.

PROJECT AIMS / OBJECTIVES

1. To define the detailed phenotype of DR15-a3135-145-specific CD4+ T cell subsets in health and disease, in HLA-transgenic mice and humans:
- Multi-colour flow cytometry panels developed to consistently identify memory subsets and chemokine receptor expression of T cells in the blood of patients with Goodpasture disease, and in a relevant HLA-transgenic mouse system.
- HLA-peptide tetramer staining techniques developed and refined for identification of antigen-specific T cells in above subsets
-Used these techniques to contribute to a collaborative project investigating liposome technology as a therapy for autoimmune disease (see below publication)
-Used these techniques to characterise the antigen-specific T cell repertoire in 16 patients with Goodpasture disease and 6 healthy controls (selected for oral presentation at international conference, as detailed below)

2. To characterise in detail the DR15-a3135-145-specific T cell receptor repertoire in immunized HLA-transgenic mice
- Single autoreactive T cells from immunized HLA-transgenic mice were isolated using techniques described in Aim 1, and T cell receptors sequenced using a multiplex PCR technique.
-Detailed analysis of the T-cell receptor repertoire demonstrated clonal expansion with significant overall diversity.
3. To establish an in vivo model of autoimmunity in which to evaluate the capacity of a3135-145-specific Tregs to modulate autoimmunity
- Successfully developed a reproducible in vivo adoptive transfer model of measurable CD4+ T cell autoimmunity to a3135-145 in lymphocyte-deplete (Ragl-/-) mice.
- Designed and executed an initial experiment to investigate the capacity of regulatory T-cells to modulate the autoimmune response.

SIGNIFICANCE AND OUTCOMES

Goodpasture disease, with its defined autoantigen and relevant animal model systems, provides a valuable opportunity to study the mechanisms of autoimmunity more broadly. This project, focusing on antigen-specific cells and their interaction with HLA-peptide complexes, has provided some new insights into the nature of cell-mediated immune responses. Understanding how tolerance to our self-proteins is maintained and lost is an important step in the development of more targeted, less toxic therapies for autoimmune diseases.

PUBLICATIONS / PRESENTATIONS

Kate J. Robson, Maliha A. Alikhan, Jia Jia Lim, Hugh H. Reid, Jamie Rossjohn, A. Richard

Kitching. CD4+ a3135-145-specific T cells in human Goodpasture Disease are enriched for

Tscm and Thl cells. Abstract accepted for oral presentation and poster, 20th International Vasculitis and ANCA Workshop, April 2022.

Alikhan MA, Jaw J, Shochet LR, Robson KJ, Ooi JD, Brouwer E, Heeringa P, Holdsworth SR,

Kitching AR. Ageing enhances cellular immunity to myeloperoxidase and experimental antim yeloperoxidase glomerulonephritis. Rheumatology {Oxford). 2021

Robson KJ, Kitching AR., Recurrent membranous nephropathy after transplantation: Donor antigen and HLA converge in defining risk. Kidney International 2021 99(3) 545-548.

Robson KJ, Kitching AR., Tertiary lymphoid tissue in kidneys: understanding local immunity and inflammation. Kidney International 2020 98(2) 280-283.

Galea R, Nel HJ. Talekar M, Liu X, Ooi JD, Huynh M, Hadjigol S, Robson KJ et al., PD-Ll- and calcitriol-dependent liposomal antigen-specific regulation of systemic inflammatory disease. JCI Insight 2019 4{18):el26025.

Robson KJ, Ooi JD, Holdsworth SR, Rossjohn J, Kitching AR., HLA and kidney disease: from associations to mechanisms. Nat Rev Nephrol 2018 14(10) 636-655.

ACKNOWLEDGEMENTS

RACP Foundation funding acknowledged in writing in the following publications:

Ali khan MA, Jaw J, Shochet LR, Robson KJ, Ooi JD, Brouwer E, Heeringa P, Holdsworth SR, Kitching AR. Ageing enhances cellular immunity to myeloperoxidase and experimental antim yeloperoxidase glomerulonephritis. Rheumatology (Oxford). 2021

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and HLA converge in defining risk. Kidney International 2021 99(3) 545-548.

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Robson KJ. Ooi JD, Holdsworth SR, Rossjohn J, Kitching AR., HLA and kidney disease: from associations to mechanisms. Nat Rev Nephrol 2018 14(10) 636-655.

And in writing during oral presentations including:

Monash University Centre for Inflammatory Diseases Seminar Series September 2021

Monash University PhD Milestone Presentations 2020 & 2021