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PhD Project Plan

Bi-directional immuno-modulation by Matrix Metalloproteinase-7 (MMP-7) and A Disintegrin And Metalloproteinase-17 (ADAM-17) as transplantation rejection-tolerance spectrum

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Abstract

Theoretically, Matrix Metalloproteinase-7 (MMP-7) leads to allograft rejection, and A Disintegrin and Metalloproteinase-17 (ADAM-17) results in allograft tolerance. The research proposal utilizes the animal model of knock-out mice to perform transplant surgery and then detect or measure allograft rejection by selected serum biomarker and tissue typing. Comparisons will be made for knock-out, wild-type, and wild-type treated with proteinase inhibitors. Methodological and theoretical details will be elucidated and revised as the research goes on.

Keywords

Matrix Metalloproteinase-7 (MMP-7), A Disintegrin And Metalloproteinase-17 (ADAM-17), transplantation, rejection, allograft

Objectives, Concept and Approach

Objectives:

1. Transplant immunity spectrum measures from none (tolerance) to full (rejection);
2. Immuno-modulator drugs that does not only suppress but also enhance immunity in transplant.

Concept

Currently, we only have immuno-suppressants (Neoral; Tacrolimus; Cellcept, etc.) “Sew-saw” roles of MMP-7 and ADAM-17 can up- (Gill et al. 2016, Li et al. 2002, Ra et al. 2009, Yu et al. 2002, Yu and Woessner 2001) and down-regulate immunity (Esteso et al. 2014, Isernhagen et al. 2016, Platt et al. 2015, Ra et al. 2009) more timely, to better overcome infection events in post-transplant patients.

We can quantify post-transplant patients’ immunity status and adjust bi-directionally the immunity levels whenever rejection or infection occurs.

- Current clinical practice only has immuno-suppressant, such as Neoral, Tacrolimus, Cellcept, but no immuno-enhancers. Infection becomes worrisome whenever immune is over-suppressed.
- Prior studies have shown that MMP-7 promotes rejection (immuno-enhancer) and ADAM-17 promotes tolerance (immuno-suppressant) (Yu et al. 2002, van Zandbergen et al. 1999).
- Our lab have established animal model of knockout (KO) mice (MMP-7; ADAM-17), and qualified proteomics/degradomics facilities.
- The immuno-modulatory mechanism of MMP-7 and ADAM-17 in transplant is still a hypothesis (Yu and Woessner 2000, Yu et al. 2012)

Approach

Animal model of transplant surgery; protease epitopes quantification and analysis; proteomics, degradomics; immune synapses networks.

Project description

1. Animal model: protease gene-knockout (KO) and wild-type (WT) mice;
2. Surgery: transplantation of s specified organ, such as kidney, heart, aorta, lungs, etc.
3. Measurement of rejection (cellular, humoral, acute, subacute, chronic?) by serum biomarker and tissue typing;
4. Data collection and analysis: proteomics, degradomics, statistical modeling;
5. Drafting of immune synapse networks from MMP-7 and ADAM-17.

Implementation

Methodology

1. Transplant surgery on KO- and WT-mice;
2. Measurement of rejection by serum marker and tissue typing;
3. Degradomics analysis;
4. Repeat the above steps 1 to 3 on mice treated with protease inhibitors;
5. Repeat the experiment on MMP-7 and ADAM-17 mice;
6. Repeat the whole experiment for replicability and reproducibility;
7. Results interpretatiom and report writing.

Work plan

The research will be carried out with the mentorship of Dr. Wei-Hsuan Yu, PhD, Laboratory of Matrix Biology, Institute of Biochemistry and Molecular Biology, College of Medicine, National Taiwan University, Taipei, Taiwan.

1. Decision of which organ to transplant on mice;
2. Decision of which serum marker and tissue typing to use;
3. Repeat the experiment for MMP-7 and ADAM-17;
4. Repeat the whole experiment for replicability and reproducibility;
5. Analysis and interpretation;
6. Report writing and publication.

Details for replicability and reproducibility

To achieve replicability and reproducibility, we will repeat the same surgery, sample collection, lab analysis, and statistical analyses on at least two individual mice. If time and funding permit, we will repeat the experiment on more mice.

Timeline

Systematic review of knowledge: 2 months;

Animal model for transplant and rejection: 4 months;

Experiment: 6 months;

Troubleshooting (buffer): 2 months;

Interpretation: 4 months;

Thesis writing: 4 months.

Data resources

1. (1) Matrix biology database (Launay et al. 2015)
2. (2) Experimental data obtained from our animal model and degradomics will be compared and explored with the use of MatrixDB (Launay et al. 2015)

Expected results and impact

Expected Results

- MMP-7 shedding products are detected in transplant rejection, or MMP7-wild type (WT) mice;
- ADAM-17 shedding products are detected in transplant rejection, or ADAM17-KO mice;
- MMP7-KO mice have no rejection, similar to MMP7-WT mice treated with MMP7-inhibitor.
- ADAM17-WT mice treated with ADAM17-inhibitor have minimal rejection.

Impact

MMP-7 inhibitor will suppress rejection and ADAM-17 inhibitor will enhance immunity. Whenever there is suspicious or confirmed rejection event, we can use MMP-7 inhibitor to rescue allograft. If there are signs of infection, we can use ADAM-17 inhibitor to conquest pathogens by upgraded immunity.

Acknowledgements

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Funding program

Pending.

Project

Shedding of MMP-7 and ADAM-17 will be analyzed and reported. Effect of proteases and their inhibitors on KO-and WT-mice on detected ejection will be assessed.

Hosting institution

Biochemistry & Molecular Biology, National Taiwan University College of Medicine, Taipei, Taiwan;

Cardiovascular Surgery, Taipei Tzuchi Hospital, New Taipei City, Taiwan;

Tzuchi University College of Medicine, Hualian, Taiwan.

Ethics and security

Institutional Animal Care and Utilization Committee (IACUC) will review and approve the proposal. The whole research will comply with the guidelines with IACUC approval.

Author contributions

Chen RJ: systematic review, study design, methodology, proposal writing; transplant surgery on mice, data sampling, lab analysis, statistical analysis.

Conflicts of interest

None.

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