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# Transplantation Immuno-Modulatory Roles of Matrix Metalloproteinase-7 (MMP-7) and A Disintegrin and Metalloproteinase-17 (ADAM-17) For Allograft Rejection-Tolerance

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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 in situ hybridization. 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.

## Motivation

End-stage organ failure has been a limiting factor for human survival and quality of life. Mechanical support may provide temporary supports in the setting of donor shortage. Allo-transplantation is still the ultimate therapy for failing organs. Regardless organ or tissue types, such as heart, lungs, kidneys, liver, pancreas, intestine, cornea, bones, etc., even with the advancement of immunosuppressant drugs such as Cyclosporine and Tacrolimus, the most

common and troubling challenge is still allograft rejection, which leads primary graft dysfunction (PGD). Exploring further into the clinical lexicons of hyperacute, acute, subacute, chronic, cellular, and humoral rejection, there are some fundamental sub-cellular and molecular mechanisms that modulate immune responses.

My recent review of a manuscript about biomarkers on PGD of lung transplant on *American Journal of Respiratory Critical Care* triggers my curiosity of the interplaying mechanisms of allo-graft rejection (**Figure 1**). Dr. Wei-Hsuan Yu and I wrote the invited editorial that briefly discussed the rejection biomarkers. Among them, the lesser known area arena is multi-functional extracellular matrix related proteinases. Matrix metalloproteinase-7 (MMP-7) and A disintegrin and metalloproteinase-17 (ADAM-17) have fewer well-done research on allograft rejection. Dr. Yu's lab facilities and knock-out mouse animal model are well-qualified for studying their immuno-modulatory roles on allograft. Therefore, I plan to seek the PhD and uncover the myths.

## Backgrounds

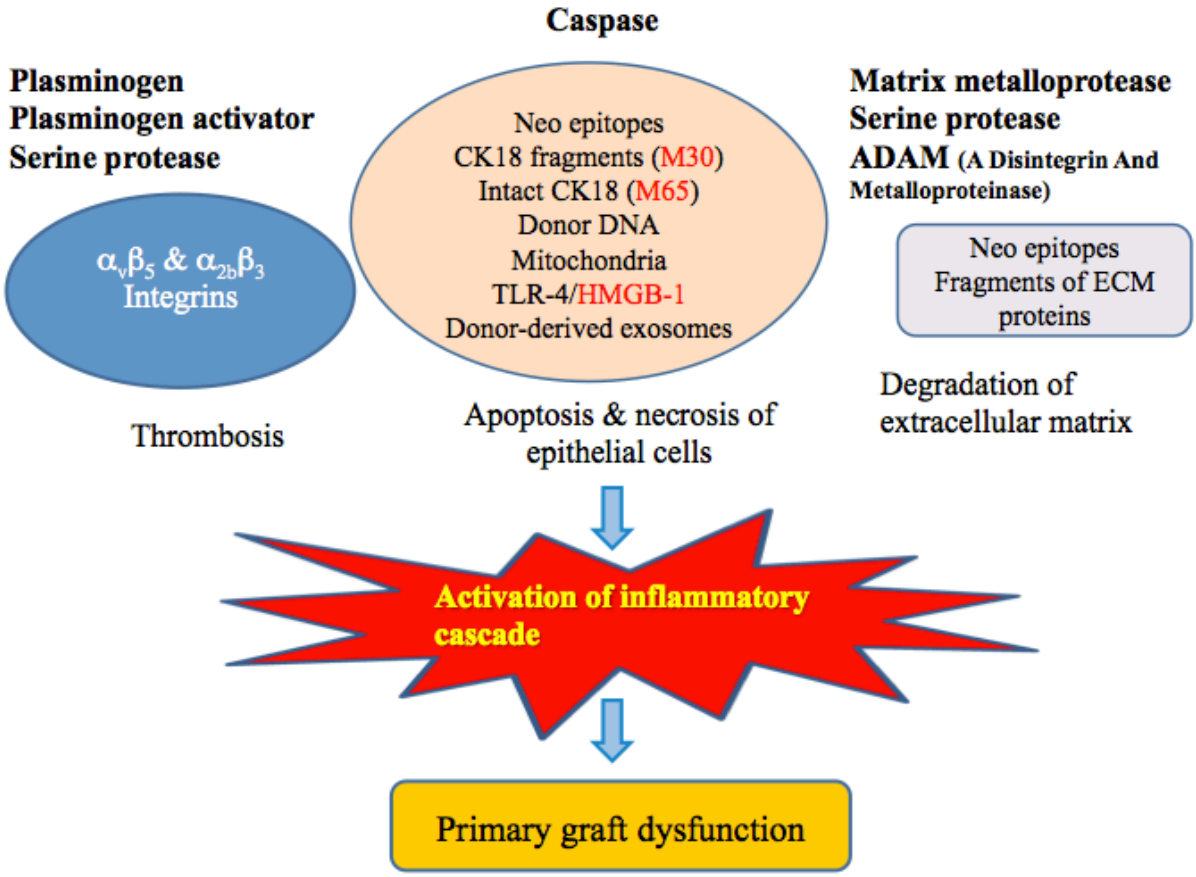


Figure 1 Schematic representation of selected pathways leading to allograft rejection, or primary graft dysfunction, showing available and potential biomarkers

Matrix biology [1] represents an array of multi-functional matrix metalloproteinases (MMP) [2]. A disintegrin and metalloproteinase (ADAM) is another family of matrix proteinases [3,45,6]. They have roles in cancer biology, wound healing, aortic aneurysm, etc. [4,7,891011] Their transplant-related roles have also been reported[121314,15]. Most of the studies are on MMP-1, -2, -3, -8, -9, and -13, and ADAM-10 and -19. MMP7 and ADAM17 have effect on leukocytes trafficking [1] and hence must have roles in immuno-modulation and allograft rejection.

Just as immune synapses acting like a sew-saw, Matrix Metalloproteinase-7 (MMP-7) up-regulates and A Disintegrin and Metalloproteinase-17 (ADAM-17) down-regulates immunity. Hence MMP-7 leads to rejection and ADAM-17 results in tolerance, acting like a "sew-saw" mechanism.

I plan to explore the mechanisms and build the functional networks of immune synapses from MMP-7 and ADAM-17.

## Aims

1. Systematic review of MMP and ADAM and further MMP7 and ADAM17, focused on but not limited to transplant;

2. Hypotheses of the mechanisms of MMP7 and ADAM17 on allograft rejection;

3. Proof of the association of MMP7 and ADAM17 with allograft rejection;

4. Proof of the association MMP7 and ADAM17 with immuno-modulation;

5. Building of the mechanism network of MMP7 and ADAM17 on allograft rejection;

6. Proposal of potential targets for drug therapy as MMP7 and ADAM17 inhibitors;

7. Proof of the efficacy and safety of MMP7 and ADAM17 inhibitors.

## Methods Outline

1. Literature review and summary of known facts of MMP7 and ADAM17;

2. Setup of animal model of allograft rejection by knockout (KO) and wild-type (WT) mice;

(1) Surgery of transplant; Which organ? Kidney? Heart (needing cardiopulmonary bypass)?

(2) Detection of allograft rejection definition and measurement; Serum biomarker (which one?); in situ hybridization (which one?); Degradomics [16] [17] [18]

3. Comparisons of transplanted KO-, WT-, and WT-inhibitor (WT-mice treated with proteinase inhibitor) mice, for allograft rejection as defined and measure above;

(1) Lab experiment;

(2) Repeating for statistical power if needed;

4. Exploration of other related MMP, ADAM, or molecules; molecular mechanism network validation.

## Expected Results

Since MMP7 and ADAM17 are physiological proteinases that involve in allograft rejection, the KO-mice should have less allograft rejection then WT-mice. WT-inhibitor mice should have similar response as KO-mice.

Intuitively, MMP7 inhibitor and ADAM17 inhibitor may be potential immuno-suppressant drugs in the future if their immuno-modulatory roles are proved in the research.

## Timetable

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.

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