Engineered immunomodulatory accessory cells improve experimental allogeneic islet transplantation without immunosuppression

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Speaker: En-Ru Liu Advisor: Ming-ko Chiang

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1.簡述論文的概要與重大發現

糖尿病在現今社會中日漸流行，而選擇做移植手術是目前最主要治療糖尿病的選擇之一。但此方法有所限制，會受限於一些與移植相關的免疫排斥，與所打的免疫抑制劑副作用過大等問題，所以如何既避免施打免疫抑制劑，又能降低排斥，是現階段的主要目標。因此就想到，利用免疫檢查點，PDL-1、CTLA4 的發現。透過，在 mesenchymal stromal cells (MSCs)中 overexpression PDL-1。這種修飾後的細胞又稱為 eMSCs (engineered MSCs)。將 eMSCs 與 islet 一同移植到糖尿病小鼠中，發現確實改善了移植排斥的結果。最後，更探討了，移植物排斥較低的原因，是因為移植物中的 T_{reg} 細胞比例較多，而導致的。

2.對論文內容的疑問

文章中，在探討移植排斥時，說明了 eMSC 的免疫調節作用。之後，為了瞭解，此免疫反應是全身性的或局部的，就將 BALB/c 小鼠的 islet 與 eMSC 一同移植到同一隻糖尿病 C57BL/6 小鼠的兩顆腎臟中。發現小鼠血糖短時間內超出正常值，證實了移植物被排斥。因此說明，eMSC 對移植在不同腎臟中的 islet 沒有排斥反應減緩的現象，而證實此種免疫調節是種局部現象。但，造成此現象之機制與解釋仍有待我多了解。

3..論文的缺點與評論

這篇文獻做了各種實驗來證實，讓細胞 overexpression PDL-1，讓 PDL-1 能跟 T 細胞上的 PD-1 binding，而去達到抑制 T 細胞活性的效果，而降低排斥反應並提高移植率，更分析了減緩排斥的原因就是 T_{reg} 細胞表現增加。最後，因為這篇 paper 所做的移植是從腎囊進去，跟臨床中的肝門靜脈移植不一樣。所以或許未來有望將研究應用於臨床上的肝門靜脈移植技術中，往臨床更進一步。

HEALTH AND MEDICINE

Engineered immunomodulatory accessory cells improve experimental allogeneic islet transplantation without immunosuppression

Xi Wang[1], Kai Wang[2,3], Ming Yu[4], Diana Velluto[5], Xuechong Hong[2,3], Bo Wang[1], Alan Chiu[1], Juan M. Melero-Martin[2,3,6], Alice A. Tomei[5,7,8], Minglin Ma[1]*

Islet transplantation has been established as a viable treatment modality for type 1 diabetes. However, the side effects of the systemic immunosuppression required for patients often outweigh its benefits. Here, we engineer programmed death ligand-1 and cytotoxic T lymphocyte antigen 4 immunoglobulin fusion protein–modified mesenchymal stromal cells (MSCs) as accessory cells for islet cotransplantation. The engineered MSCs (eMSCs) improved the outcome of both syngeneic and allogeneic islet transplantation in diabetic mice and resulted in allograft survival for up to 100 days without any systemic immunosuppression. Immunophenotyping revealed reduced infiltration of $CD4^+$ or $CD8^+$ T effector cells and increased infiltration of T regulatory cells within the allografts cotransplanted with eMSCs compared to controls. The results suggest that the eMSCs can induce local immunomodulation and may be applicable in clinical islet transplantation to reduce or minimize the need of systemic immunosuppression and ameliorate its negative impact.

INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune disease in which immune cells (mainly $CD8^+$ T cells) mistakenly attack β cells, causing deficiency of insulin and elevation of blood glucose. Replacement of β cells by allogeneic islet transplantation via portal vein has been established in clinics all over the world and shown to improve glycemic control among patients (*1*, *2*). However, systemic immunosuppression, required to prevent allograft rejection, may be toxic to islets and, more importantly, has deleterious side effects to patients (*3*, *4*). Of note, for most T1D patients, the systemic immunosuppression is riskier than long-term standard management with exogenous insulin supplementation, which makes eliminating systemic immunosuppression critical to β cell replacement therapies. Novel strategies to circumvent the challenges associated with systemic immunosuppression have been extensively pursued for islet transplantation recently including immunoprotection using cell encapsulation devices (*5*–*8*) and induction of local immunotolerance toward allogeneic islets (*9*). Compared to cell encapsulation, the local immunomodulation approach is considered as "open," involving no physical barrier between the graft and the body and therefore can potentially allow better and direct host integration.

In general, T cells play a critical role in allograft rejection (*10*, *11*). Upon recognition of alloantigens, a costimulatory signal, commonly provided by B7-1 (CD80) or B7-2 (CD86) ligands on antigen-presenting cells (APCs) that interact with CD28 on T cells, is necessary for T cell activation (*9*). Thus, modulation of T cell costimulatory pathways, including blocking T cell costimulation and/or providing negative modulatory signals, has been investigated and used to improve graft survival and functionality. Specifically, the programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) interaction is a well-studied negative costimulatory pathway, which is critical in maintaining peripheral tolerance and immunological homeostasis (*12*). Targeting the PD-1/PD-L1 pathway was shown to regulate and delay immune destruction of allograft in cardiac (*13*, *14*), islet (*15*), and corneal (*16*) transplantation. Similarly, the cytotoxic T lymphocyte antigen 4 immunoglobulin (CTLA4-Ig) fusion protein, which competitively blocks the CD28-B7 pathways, was shown to inhibit T cell activation (*17*) and prevent allograft rejection in skin (*18*), cardiac (*19*, *20*), liver (*21*), and islet (*22*, *23*) transplantation. In addition, PD-L1 and CTLA4-Ig have been demonstrated to inhibit T cell activity in a nonredundant way (*24*, *25*). Despite these promising developments, the PD-L1 or CTLA4-Ig was often administered systemically and cause nonspecific immune responses and immune-related toxicity (*26*). Thus, there is great interest in targeted delivery of immunomodulatory molecules and localized regulation of immune responses within the graft microenvironment.

Multiple studies have reported strategies of using the PD-L1 or CTLA4 immune checkpoint pathways to improve islet transplantation in a localized manner. For example, researchers engineered functional biomaterial platforms [poly(ethylene glycol) (PEG) microgels] to display PD-L1, which have been shown to achieve long-term allogeneic islet graft function in diabetic mouse models with a short-term (15 days) administration of rapamycin (*27*). A major advantage of the biomaterial approach is that the biomaterial can be prefabricated, and there is a minimal need, if any, to manipulate or modify the islets. However, biomaterials can cause foreign body responses and induce antibodies (e.g., anti-PEG antibodies) and may be challenging to be applied in current clinical islet transplantation through the portal vein. In addition, the immunomodulatory ligands delivered or presented via biomaterials may degrade or be depleted over time. Alternatively, mouse islets were modified with PD-L1/CTLA4-Ig (*28*) or PD-L1 (*29*, *30*), which resulted in protection of islets from acute rejection. Although modifying islets is a straightforward

[1]Department of Biological and Environmental Engineering, Cornell University, Ithaca, NY 14853, USA. [2]Department of Cardiac Surgery, Boston Children's Hospital, Boston, MA 02115, USA. [3]Department of Surgery, Harvard Medical School, Boston, MA 02115, USA. [4]Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA 19104, USA. [5]Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, FL 33136, USA. [6]Harvard Stem Cell Institute, Cambridge, MA 02138, USA. [7]Department of Biomedical Engineering, University of Miami, Miami, FL 33146, USA. [8]Department of Surgery, University of Miami Miller School of Medicine, Miami, FL 33136, USA.
*Corresponding author. Email: mm826@cornell.edu