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Diabetes-Related Islet and Hematopoietic Cell Transplantation That Cures the Condition in Mice without Harmful Bone Marrow Conditioning

John Gilbert*

Department of Physiology, University of Essex, United Kingdom

Abstract

The immunological tolerance of donor-matched transplanted tissues, such as pancreatic islets, can be enhanced by mixed hematopoietic chimerism. Adoption of this approach is, however, constrained by the toxicity of conventional therapies that allow donor hematopoietic cell engraftment. Here, we address these issues by using a non-myeloablative conditioning regimen that promotes allograft tolerance and hematopoietic chimerism across totally mismatched major histocompatibility complex (MHC) barriers. Immunocompetent mice treated with a CD117 antibody that targets the c-Kit protein along with T cell-depleting antibodies and low-dose radiation are able to develop permanent multi-lineage chimerism after hematopoietic cell transplantation. Co-transplantation of donor-matched islets and hematopoietic cells effectively reverses diabetes in diabetic mice without causing persistent immunosuppression or significant graft-versus-host disease (GVHD). Allotolerance is most likely mediated by peripheral regulatory T cells produced from the host and donor-derived thymic antigen-presenting cells.

Keywords: I c era ce; I era a a ; M ed c ; Tra a fHe a ce ; Dabe e; A- e ec ra a b d ar /

Introduction

E ec . ea e f dabe e a a ea c be a-ce e ra a a f a ea c e f MHC- ac ed (a e ec) d , /e ced e ece a e - e e e ec C c e d a d T ce b a ec ee e b e a / f e a a / e e a e be da e f / de ead e e ra a a a d e e f e c c bd e. H / e , fa e f HSC e a e cc f e aba . ed d a e a e decea ed ed ce c d e e . I f , afe NMA c d c [2].

We ed B6 RIP-DTR ce e / e e a e HCT a d e a a a c d e . e d abe c ec e e . e ba e f f MHC ac . ee a e f P ca a d a e e I 2-HBEGF a e e. A e ece. a ed e f d e a (DT; STAR Me d), e be a-ce ab a ca e e e bec e e e e de de a d d abe c. P / NMA c d , a ea d fe a e B6 RIP-DTR ce / e e . e DT da 4.5 a d beca ed abe c. C d ed ce a e a a fa B6, BALB/c, / FVB e - ac ed d da 0 a d a BALB/c e - ac ed d , HCT da 0. F / a a a ce / e e b e . ed f 20 / ee (c / 1) / 16 / ee (c / 2). B 4 / ee f / e a a [4].

FVB e ec e a e e e ced e ce a, b a e a ea f 78 da (= 4; F e 3G), e a e ea ed e ce a. De c f e a a ed FVB e / a c ed b a ec . e a d ca a a . e FVB a f c a ed e a e ca 2- / ee e d f e e ec e c e e / a ce. We e e a de a ca ed b a be f. a abe , c d a a / e e a ec e , e a a e d f de . e ec / T ce , a d e a e ac be / ee e d e , e ce a d a a a ed e . H / e e , e a e ec f e a a fa ad , e e ce / ed a ed c ae a ad e a ed c e e ce [5].

Mixed chimerism increases the tolerance to allogeneic islets

We ed a / e e d - ac ed e a a e a ce / a e a ced b e e e ce f ed c e be / ee a MHC ac ed a a e NMA c d . M ce / ed c e c d ed c / e e 12.1( )8( ) c 0.M c ec / B6 a d BALB/c / d- a FVB (H2) d / de d b ac e a d - e e a ce.; I ce / ed BALB/c c e , e BALB/c e a e ed / ee a e a a a / a CD3+ T ce a a d ca ce CD45+ ece a I c / a , e a f ea ed FVB d / ad a e e f CD3+ a d CD45+ ce a Gra f BALB/c / e e [3].

Discussion

M ed e a e c c e ca d ce d / - ec c

***Corresponding author:** John Gilbert, Department of Physiology, University of Essex, United Kingdom, E-mail: Johng39@yahoo.com

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