Reversal of Severe Autoimmune Diabetes at The Stem Cell Level By Bone Marrow-derived Endothelial Progenitors

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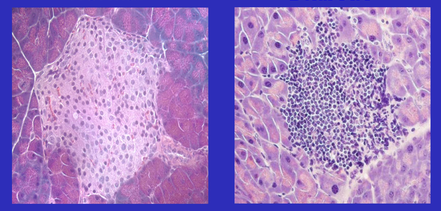
Introduction

Type 1 diabetes (T1D):

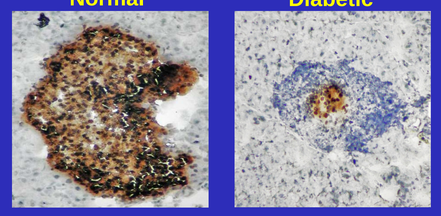
1. Autoimmune: Infiltration of lymphocytes into pancreatic islets

Normal Diabetic



2. Critical loss of insulin-producing β cells

Normal Diabetic

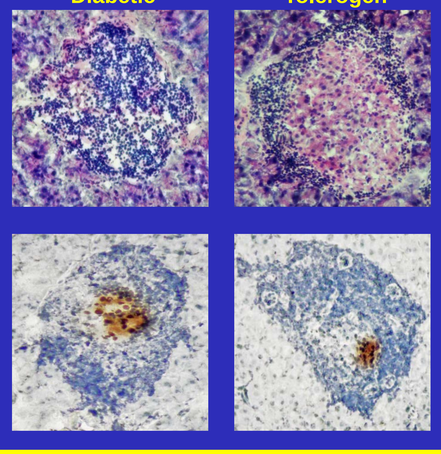


3. High blood glucose level with clinical complications:
   - Heart disease
   - High blood pressure
   - Blindness
   - Kidney failure
   - Nerve damage
   - Amputation
   - Poor vascularization

4. Classic strategy for therapy of type 1 diabetes:
   - Effective control of inflammation to facilitate β cell regeneration/ replication/ differentiation

However, only control of islet infiltration is not sufficient to reverse overt T1D

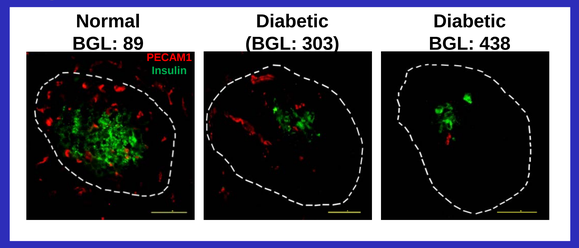
Diabetic Tolerogen



Even after tolerogen treatment that effectively inhibited islet infiltration, there is no sign of restoration of β cell mass, and these mice still maintain high blood glucose levels.

What is the problem?

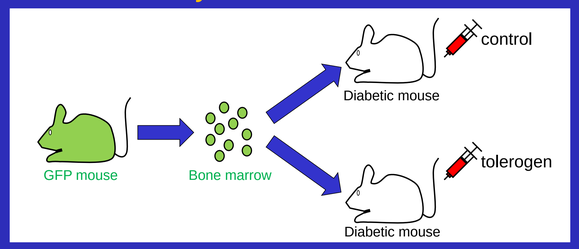
Strikingly impaired micro-vascularization in pancreatic islets in T1D



Intra-islet vascularization is essential for *in vivo* maintenance of β cells and transportation of insulin

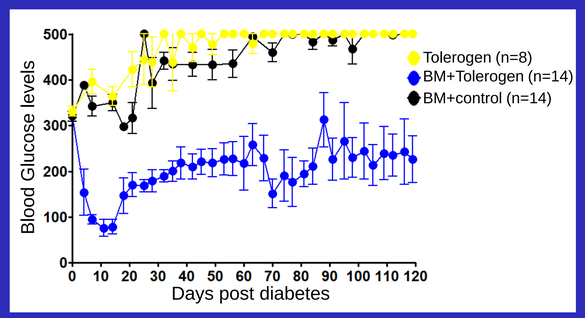
Combination strategy

Restore functional islet vascularization in diabetic mice by bone marrow transfer



Results

1. Both tolerogen and donor bone marrow are required for reversal of T1D

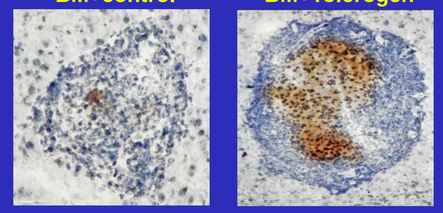


β cell regeneration in treated mice?

2. Increased β cell proliferation in treated mice

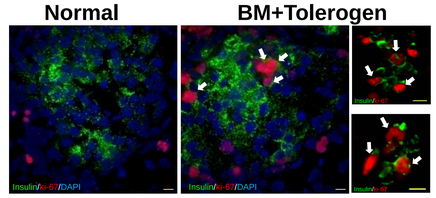
A. Increased β cell mass in treated mice

BM+control BM+Tolerogen



B. Proliferation of β cells in treated mice

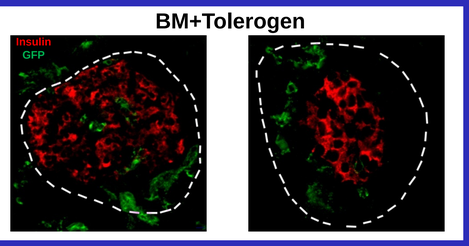
Normal BM+Tolerogen



Mechanisms underlying β cell regeneration?

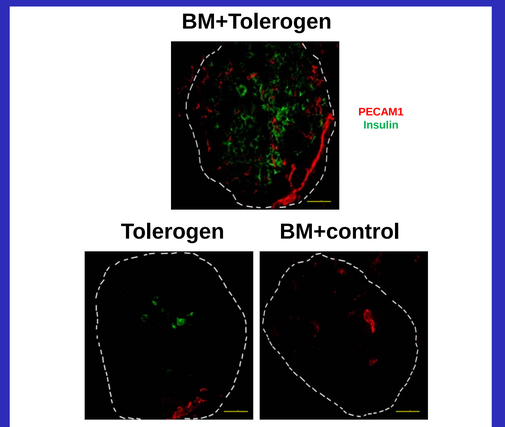
3. Donor Bone marrow derived cells do not differentiate into mature β cells

BM+Tolerogen



4. Restored intra-islet vascularization in treated mice

BM+Tolerogen



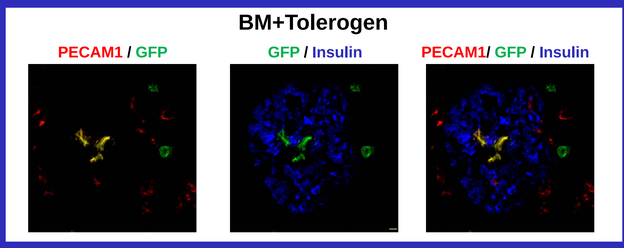
Tolerogen BM+control

Donor bone marrow-derived endothelial cells?

-This project was funded by NIH grants.

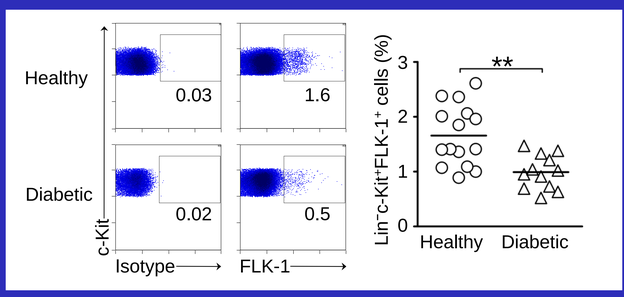
5. Donor bone marrow-derived endothelial cells in treated mice

BM+Tolerogen

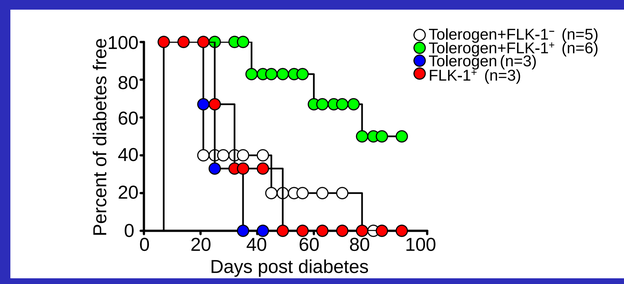


How about transfer of purified endothelial progenitors from the bone marrow?

6. Decreased endothelial progenitor cells in the bone marrow of diabetic mice



7. Transfer of purified endothelial progenitor cells instead of whole bone marrow restored T1D



Conclusions

1. Restoration of functional islet vascularization is critical for β cell regeneration
2. Control of inflammation is the basis of the protection
3. Angiogenic therapies should be combined with immunomodulatory therapies to revserse T1D.

It is time to think about autoimmune diabetes at the stem cell level!