Technical approaches to prevent β-cell apoptosis in type 2 diabetes

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β-Cell Function is a Major Contributor

ADA GENNID Study Group. Diabetes 51:2172, 2002
Technical approaches to prevent β-cell apoptosis

1. Empowerment of β-cells via systemic administration of certain substances

2. Re-arming of β-cells via direct cell modifications

3. Proliferation of existing β-cells to ameliorate the toxic environment
Natural Substances
EGCG (epigallocatechin gallate)

- Major constituent of Green Tea
- Very strong anti-oxidant (Cancer Lett 2006)

- CVD (Am J Clin Nutr 2002)

- Diabetes Mellitus
  - Lowered diabetes incidence in Japanese population
    - Ann Intern Med 2006
  - Increase insulin sensitivity in animal models
    - BMC Pharmacol 2004, JBC 2002
Protective effect of EGCG on INS-1 cell in the oxidative stress

Mi K Kim et al. Kor Diabetes J 32:121-130, 2008   EASD, 2008
Protective effect of EGCG on INS-1 cell in the oxidative stress

Mi K Kim et al. Kor Diabetes J 32:121-130, 2008  EASD, 2008
Clinical trial on type 2 diabetes using Green Tea polyphenol

Mi K Kim et al. Kor Diabetes J 30:217-225, 2006

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Green tea polyphenol*</th>
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<tbody>
<tr>
<td><strong>Body</strong></td>
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<td>BMI (kg/m²)</td>
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<td>Waist</td>
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<td>Fasting</td>
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<td>HbA1c</td>
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<td>Total cholesterol</td>
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<td>HDL cholesterol</td>
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<td>Triglycerides</td>
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<td>AST (unit/L)</td>
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<td>γ-GT</td>
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<td>Serum</td>
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<td>Urine</td>
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Values are means ± standard deviations.
Quercetin

• Flavonoid (3,5,7,3,4-pentahydroxyflavone)

• Very strong anti-oxidant, enhance anti-oxidative defense
  Inhibition of free radical (Diabetes, 1997)
  Inhibition of lipid peroxidation (Free Radic Res, 2001)
  Inhibition of xanthine oxidase (Redox Rep, 1999)

• Diabetes Mellitus
  Effects on chronic diabetic complications
  Curr Opin Endocrinol Diabetes Obes, 1996
  Diabetes Care, 2003
Cytoprotective effect of Quercetin on INS-1 cells

Cytoprotective effect of Quercetin on INS-1 cells

Cytoprotective effect of Quercetin on INS-1 cells

The actions of EGCG & Quercetin on INS-1 cells are different

Mi K Kim et al. Frontiers in Bioscience (Elite Ed) 2010
The actions of EGCG & Quercetin on INS-1 cells are different

Mi K Kim et al. Frontiers in Bioscience (Elite Ed) 2010
Chromium

- Control blood glucose (Archives of Biochemistry and Biophysics, 1957)
- Weight loss, fat burning, muscle building, diabetes and cholesterol control

- Evidences for Diabetes Control

- Improving insulin resistance - apochromodulin
  - J Am Coll Nutrition, 1999
  - Biochemistry, 1997

- Reduction of oxidative stress in monocyte
  - BBRC, 2001
  - Free Radical Biology & Medicine, 2004
  - Antioxidants Redox Signalling, 2007
The Effect of Chromium on INS-1 cells in Hyperglycemia

Min J Kwon et al. Life Science 87:401-404, 2010
1. Possibilities exist

2. Systemic administration, *aiming local effect*?

3. *Other untoward effects*, while establishing localized effective concentration
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Protection of genetically modified INS-1 cell from hypoxia

Protection of genetically modified INS-1 cell from hypoxia

Sonoporation: UTMD

plasmid DNA

micro-bubble

Y Liu et al, J Cont Release, 2006
Sonoporation: UTMD

Physical Targeting + Promoter Specificity = Effective Specific Cell Targeting
Sonoporation into pancreatic β-cells: proof of concept

S Chen et al. PNAS 103(22): 8469-8474, 2006
Sonoporation into Pancreatic β-Cells: proof of concept

S Chen et al. PNAS 103(22): 8469-8474, 2006

The figure shows luciferase activity (RLU/mg protein) for different organs: pancreas, spleen, liver, left kidney, right kidney, and muscle. The y-axis represents luciferase activity, ranging from 0 to 1400. The x-axis lists the organs. The bars indicate the luciferase activity for CMV-luc, RIP-luc, and glucose + RIP-luc. The p-values are noted: p<0.0001 for pancreas vs other organs and p<0.0001 for glucose vs non-glucose.
Sonoporation into pancreatic β-cells: proof of concept

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Remission of Type 2 Diabetes

- Remission: the state of absence of disease activity in patients with a chronic illness, with the possibility of return of disease activity (www.wikipedia.com)

- Remission of type 2 diabetes

1. Metformin monotherapy small to medium dosage mean HbA1c below 6.5%

2. Multiple insulin injection with oral agents mean HbA1c over 8.0%

Holman RR. DRCP 1998:40(S);S21-S25
Regeneration of islets via targeted sonoporation

PA Grayburn et al. Gene Therapy, 2010
Regeneration of islets via targeted sonoporation

PA Grayburn et al. Gene Therapy, 2010
Regeneration of islets via targeted sonoporation

PA Grayburn et al. Gene Therapy, 2010
Why stick to the β-cells as a target?

- Low numbers, decreased cell activity of β-cells in diabetes
  - suppressed insulin gene transcription
  - **NOT SO GOOD** candidate for gene transfection

Paracrine connection between $\alpha$ and $\beta$-cells

Red: $\beta$-cells
Green: $\alpha$-cells

D Bosco et al. Diabetes 59:1202-1210, 2010
Paracrine connection between $\alpha$ and $\beta$-cells

Red : $\beta$-cells  Green : $\alpha$-cells

D Bosco et al. Diabetes 59:1202-1210, 2010
Our on-going project

*Sonoporation GLP-1 gene therapy for the remission of advanced type 2 diabetes*

- Sonoporation for the delivery of therapeutic gene (GLP-1), the most safe and convenient method of gene therapy

- GLP-1, rather than exendin-4 and other growth factors, for utilizing localized DPP-IV to prevent the spill over effects on the exocrine pancreas

- Target cells: overly active and proliferated α-cells, rather than the small numbers of tired β-cells, using glucagon promoter system
We thank for the generous research grants from
1. Inje University
2. Korean Diabetes Association
3. Ministry of Health and Welfare
4. National Research Foundation of Korea
5. Pharmaceutical Companies, including sanofi-aventis etc.