The Pancreas in Type 1 Diabetes

Does enteroviral infection of beta cells precipitate their autoimmune destruction?

Alan K. Foulis
Sarah J. Richardson
Insulitis in Type 1 Diabetes
Type 1 diabetes

- Organ specific autoimmune disease
- 85% of patients have islet cell antibodies at presentation
- Beta cell destruction takes place over a prolonged period of time
- Diabetes develops when 80% of beta cells have been destroyed
Type 1 diabetes - Genetics

- Up to 98% of patients are HLA DR3 or HLA DR4
- Even stronger association with DQ alleles (HLA-DQB1)
- Concordance rate in monozygotic twins only 30%
Type 1 Diabetes – Increasing Incidence

• Incidence doubling every 30 years

• The incidence is rising particularly quickly in children under the age of 5
Type 1 diabetes - Enteroviruses

- Coxsackie B virus cultured from the pancreas of one diabetic child. The virus caused diabetes when injected into mice.

- 30% of newly diagnosed diabetic patients and 5% of controls have IgM antibodies to Coxsackie B virus.

- 27% of newly diagnosed diabetic children and 5% of controls have enteroviral RNA in serum at diagnosis.

- 51% of pre-diabetic children have evidence of enteroviral infection in the 6 months before autoantibody seroconversion compared with 28% in controls.
Type 1 Diabetic Pancreas Collection

- Computerised records of death certificates in UK over 25 year period of patients, <20 years, dying of diabetes, who had an autopsy.

- Paraffin embedded blocks of pancreas requested.

- Material from > 70 cases where death occurred at the time of first clinical diagnosis of diabetes.
Cumulative Number Of Cases Available For Study

Cumulative No of Pancreata available for histopathological research

UK Cohort

1902-2010

Insulin
Islet Pathology in Type I Diabetes

- Insulin deficient islets
- Insulin containing islets with insulitis
- Insulin containing islets without insulitis
- Beta cells have been destroyed
- Beta cells are being destroyed
- Beta cells have yet to be destroyed
Possible Sequence of events in islets in Type 1 diabetes

- Insulin containing islet
- Insulitis
- Destruction of B cells
- Insulin deficient islet
Insulitis in Type 1 diabetes

Willcox CEI, 2009

Decreasing insulin content

Mean No. Cells/Islet Section

CD4 T cells
CD8 T cells
CD20 B cells
CD68 Macrophages
Type 1 Diabetes

• Are there abnormalities of class I MHC expression?
Class I MHC
Class I MHC
Insulin
Glucagon
Class I MHC
Possible sequence of events in islets in Type 1 diabetes

1. Hyperexpression of class I MHC by insulin containing islet
2. Insulitis
3. Destruction of B cells
4. Insulin deficient islet
Class I MHC Expression in Control Pancreases

• No comparable hyperexpression of class I MHC seen on pancreatic endocrine cells in
  - Normal autopsy pancreas
  Type 2 diabetes
  Cystic fibrosis
  Chronic pancreatitis
  Graft versus host disease
  Neonatal Coxsackie B viral infection
Agents known to cause hyperexpression of Class I MHC on islet endocrine cells *in vitro*

- Interferon-alpha
- Interferon-beta
- Interferon-gamma
Interferon-alpha
Insulin
Interferon-alpha
Insulin

Interferon-alpha
Possible sequence of events in islets in Type 1 diabetes

1. Secretion of IFN-alpha by B cells
2. Hyperexpression of class I MHC
3. Insulitis
4. Destruction of B cells
5. Insulin deficient islet
Interferon-alpha in islets in control pancreases

• No significant interferon-alpha in
  
  Normal pancreas
  Graft versus host disease
  Chronic pancreatitis
  Type 2 diabetes
Neonatal Coxsackie B viral pancreatitis
Neonatal Coxsackie infection

Enteroviral VP-1
Coxsackie viral infection

Interferon-alpha

Insulin
Possible sequence of events in islets in Type 1 diabetes

Normal islet → Viral infection of B cells? → Secretion of IFN-alpha by B cells → Hyperexpression of class I MHC → Insulitis → Destruction of B cells → Insulin deficient islet

Path Soc Oakley Lectureship Oxford 1987
# Viral studies on diabetic pancreases 1990

<table>
<thead>
<tr>
<th>Virus</th>
<th>Techniques Used</th>
<th>Pancreases studied</th>
<th>No. positive</th>
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<tbody>
<tr>
<td>CMV</td>
<td>PCR</td>
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<td>Mumps</td>
<td>ICC</td>
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</tr>
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<td>EBV</td>
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</tr>
</tbody>
</table>
Technical Developments

• New monoclonal antibody to enteroviral VP-1: Dako 5D8/1

• Antigen retrieval on formalin fixed paraffin embedded tissues