A Distinct Population of Islet Cells Defines Diffuse Congenital Hyperinsulinism in Infancy but Not Other Forms of the Disease

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Background

Congenital Hyperinsulinism in Infancy (CHI) mainly arises due to mutations in ATP-sensitive K-channel genes (ABCC8 and KCNJ11). However, the expression pattern of defects can be markedly diverse. In diffuse CHI (CHI-D) all islet cells express gene defects, whereas patients with focal CHI (CHI-F) only express defects in a localised region of pancreas due to loss of a maternally-imprinted locus. Islet cell nuleomegaly – enlargement of the nucleus, has been described in association with CHI-D, but not CHI-F nor a novel form of the disease – atypical CHI (CHI-A). Our objectives were (1) to quantify islet cell nuleomegaly, (2) assess the incidence of nuleomegaly in control and CHI tissues, and (3) examine the association of nuleomegaly with proliferation.

Methods

Tissue was obtained following surgery from patients with CHI-D (n=9 patients with ABCC8/KCNJ11 gene defects), CHI-F (n=5 patients with ABCC8 gene defects), CHI-A (n=3 patients with unknown genetic causes of disease) and age-matched controls (n=8, 2-months to 36-months of age). High-content analysis of histological sections (5 µm) and serial block face-scanning electron microscopy were used to quantify nuleomegaly and determined the extent of nuleomegaly in islets and islet cells.

Results 1 – The Magnitude of Islet Cell Nucleomegaly

Typical images of nuleomegaly (arrowheads) in islets (dotted lines). Tissue sections were stained using the proliferation marker, Ki67 (filled arrows). Scale bar = 40 µm. The histograms provide a summary of nuclei surface area in CHI and control cells. (i) Distribution ranges of nuclear areas for endocrine control, exocrine control and nuleomegaly cells. (ii) Summary of the average areas of enlarged nuclei in islet cells with nuclei in both endocrine and exocrine cells. **p<0.001.

Results 2 – Nucleomegaly is Found in Endocrine Cells

The nucleus has been imprinted with a variety of defects. Image series from serial block face-scanning electron microscopy through adjacent parts of the same tissue. Note the limited number of secretory granules which were found in the cell with nuleomegaly (N). Typical secretory granules are indicated by the arrows and shown in more detail in the expanded image in section 30. Note how extensive secretory granules are in the surrounding cells and in the control cell illustrated in the right-hand montage (C). For this dataset each image is separated by 1 µm. Scale bar = 2 µm; expanded image = 500 nm.

Results 3 – Nucleomegaly and the Diversity of CHI

The incidence of islet cell nuleomegaly. (A) Incidence of nuleomegaly cells in the population of islet cells from CHI and age-matched control. ***p<0.001. (B) Incidence of nuleomegaly-positive cells in islets. **p<0.001; ***p<0.0001. (C) The range of enlarged nuclei observed in islets for each cohort and the age-matched control group.

Results 4 – Nucleomegaly and Cell Proliferation

Summary of the percentage of islet cells with nuleomegaly that were also positive for the proliferation marker, Ki67. Note that only CHI-D islets have a negative correlation with proliferation.

Conclusions

Islet cell nuleomegaly is a normal feature of the post-natal pancreas. Whilst cells with enlarged nuclei are pathognomonic for CHI-D and not other forms of disease, these cells are negatively associated with proliferation in diffuse disease suggesting a novel role in the pathobiology of this condition.

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