Tissues, Pathology, and Diagnostic Microscopy

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Ultra-large high-resolution Electron Microscopy mapping of Islets of Langerhans of Rats developing Type 1 Diabetes

R. Ravelli[1], R. Kalicharan[2], C. Avramut[1], K. Sjollema[2], J. Pronk[1], F. Dijk[2], B. Koster[1], J. Visser[2]
F. Faas[1], B. Giepmans[2]

[1]LUMC, Leiden, Netherlands
[2]UMCG, Groningen, Netherlands

raimond.nl@gmail.com
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Electron microscopy (EM) is the method to visualize tissue composition, cellular interactions and physiological conditions. However, conventional EM only covers a small area and usually lacks the context of the tissue. We present large-area EM imaging [1] that allows to characterize entire cross-sections of Islets of Langerhans during Type 1 diabetes onset [2]. In Type 1 diabetes, insulin producing beta cells are destroyed by the auto-immune system. Upon diagnosis, life-long exogenous insulin therapy is immediately initiated. However, this does not allow the fine-tuning as done by Islets, making it impossible to maintain proper glucose control, and patients cannot be cured. The causes and triggers of the disease are still unknown, yet several potential triggers have been named, including enteroviruses.

Our data [2], totaling over 25.000 electron micrographs stitched together in 6 datasets, shows the progressive destruction of the Islets of Langerhans, especially of the insulin-producing cells (Figure 1). The ultrastructural morphology allows the identification of individual cell types (Figure 2). Our datasets show leukocyte infiltration as well as damage to the organelles of the beta cells under attack, including mitochondrial damage and endoplasmic reticulum stress. Moreover, molecular abnormalities can be identified at higher zoom, including the debated rare filamentous nuclear actin [3]. Putative viral particles appearing in the beta cells are shown to be glycogen. Our technology will help to get a better insight into Islet changes at the cell, organelle, and molecular level during diabetes, but will also be applicable to numerous other tissues and diseases. The data will be made publicly accessible on electronmicroscopy.lumc.nl and www.nanotomy.nl .

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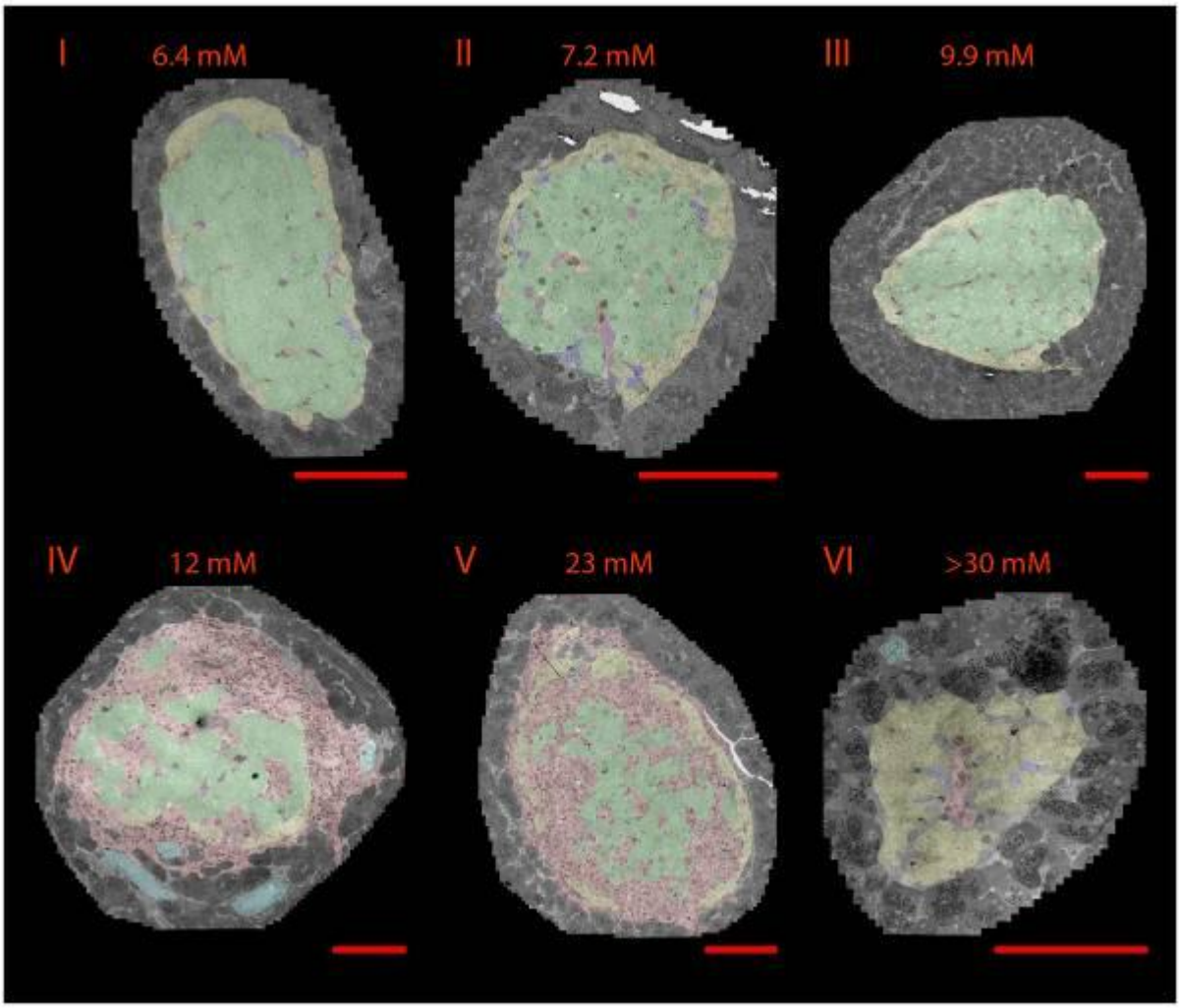

Figure 1. Islets of Langerhans during autoimmune diabetes progression. Cross-sections of entire Islets of Langerhans were acquired with a pixelsize of 3.2nm, resulting in images varying between 5 and 25 gigapixels in size. Individual cells were morphologically characterized and false-coloured according to cell-type: beta cells (green), alpha cells (yellow), leukocytes (red), ducts (purple), vasculature (cyan). (I) Diabetes resistant rat; (II)-(VI) diabetes prone rats at different stages of (pre)diabetes, as indicated by the blood sugar (BG) level. Note the massive infiltration of leukocytes (red) and the destruction of beta cells (green). Bars: 0.1mm.

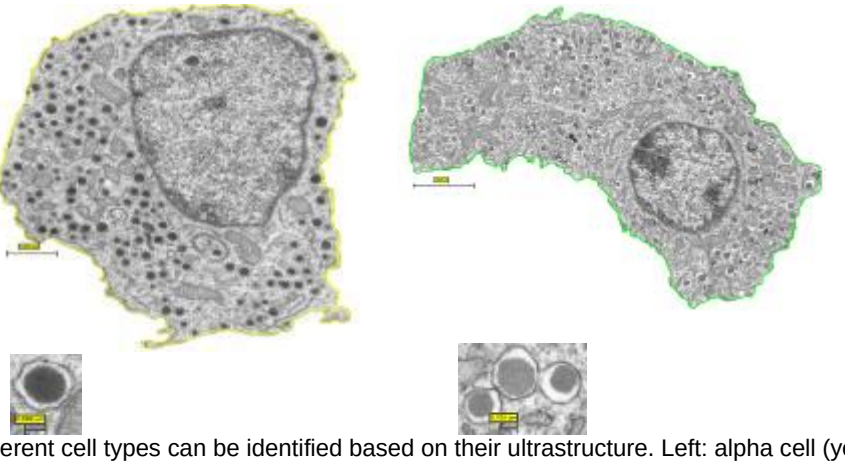

Figure 2. Different cell types can be identified based on their ultrastructure. Left: alpha cell (yellow) with granules containing darker stained glucagon; right: beta cell (green) with granules containing slightly lighter stained crystalline.