EM observations on the 3-D structure of giant mitochondria in human non-alcoholic fatty liver disease (NAFLD)

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Giant mitochondria (GM) are peculiarly-shaped, over-sized mitochondria in human hepatic parenchymal cells, the internal structure of which is characterised by atypically arranged cristae, dense granules and crystalline inclusions. The presence of GM has been documented in a variety of tissues and under various physiological and pathological conditions. Despite the diverse milieu in which GM exist, the presence of GM is often linked with cellular adversity - caused by toxins like alcohol, xenobiotics, anti-cancer drugs, free-radicals, nutritional deficiencies or as a consequence of high fat Western diets. To date, non-alcoholic fatty liver disease is the most prevalent liver disease. In lipid dysmetabolism, driven by insulin resistance, mitochondrial dysfunction plays a crucial role. It is not well understood if the morphologic changes of the mitochondria are an adaption or caused by dysfunction. Light microscopic imaging is not useful in explaining the changes in relation to function, therefore it would be interesting to study the ultrastructural changes with EM, trying to elucidate the mechanisms behind the GM development. Much of the literature concerning GM have utilised conventional two-dimensional light and/or electron microscopy techniques, providing a detailed description of the fine structure of GM. In the present study, we firstly exploited array tomography to probe large volumes of diseased human liver tissue, in order to determine the distribution and 3-D morphology of thousands of GM. Next, transmission electron tomography was complementarily employed in order to examine the ultrastructural features of GM in non-alcoholic fatty disease. Such structural findings were accompanied by 3-D morphometric data, providing a previously unseen insight into the structure of GM, and their appearance in a common human hepatic disease.