Abstract

Glucose homeostasis is crucial for the proper functioning of the organism. The pancreatic β-cells, which serve as a sensor of changes in blood glucose concentration and are responsible for the adequate release of the hormone insulin, play a crucial role in its maintenance. Increased glucose concentration activates oxidative phosphorylation and subsequently increases the concentration of cellular ATP, which then indirectly stimulates insulin secretion. The process of oxidative phosphorylation is localized in the inner mitochondrial membrane, where the final stage of processing of substrate energy into ATP occurs. To make the oxidative phosphorylation process as efficient as possible, the mitochondrial network undergoes a series of morphological changes. In this work, we aimed to elucidate the effect of changes in nutrient concentration on mitochondrial morphology in a pancreatic β-cell model, the INS1E tissue line. We used as experimental conditions: 1) a high glucose concentration at which insulin secretion is maximal, 2) a low glucose concentration at which insulin secretion does not occur, and 3) the addition of α-ketoisocaproate, a leucine metabolite that amplifies insulin secretion. We first characterized the bioenergetic parameters that influence mitochondrial morphology. A decrease in glucose concentration resulted in a decrease in cellular respiration, while an increase in mitochondrial membrane potential was observed, accompanied by an increase in the formation of reactive oxygen species in the respiratory chain. α-Ketoisocaproate showed a behavior very similar to low glucose in physiological parameters. Analysis of the mitochondrial network showed a reduction in the number of mitochondrial tubules with the widest diameters at low glucose. Transmission electron microscopy imaging of mitochondrial cristae showed their widening in low glucose and a weaker but similar effect when incubated with α-ketoisocaproate. Utilizing dSTORM microscopy, we determined under low glucose and in the presence of α-ketoisocaproate a lower clustering rate of FoF1 ATP synthase, whose oligomers are principally involved in cristae formation. Furthermore, it has been shown that OPA1 (Optic atrophy protein 1) is involved in crista remodeling and morphology of the mitochondrial network of INS1E cells at different metabolic states, and its regulation is facilitated by cleavage by the OMA1 protease.