Mitochondrial Functionality in Highly Glycolytic T98G and U-87MG Glioma Cells: Evidence for Impaired ADP Phosphorylation Despite Preserved Oxidative Capacity

Rodrigues-Silva, E.[1]; Siqueira-Santos, E.S.[1]; Ruas, J.S.[1]; Rogério, F.[2]; Castilho, R.F.[1]

[1]Dep. de Patologia Clínica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil; [2]Dep. de Anatomia Patológica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil.

ABSTRACT

Introduction: Glioma cells exhibit increased conversion of glucose to lactate even in the presence of normal levels of oxygen (Warburg effect). **Objectives:** The aim of this study was to characterize mitochondrial oxidative function of the T98G and U-87MG glioma cells. **Material and Methods:** For this proposal measurements of oxygen consumption rate (OCR) were performed. **Results and Discussion:** The addition of the protonophore FCCP to intact cells suspended in DMEM medium resulted in a sustained 2-3 fold increase in oxygen consumption, eliciting oxygen consumption rates that resembled those of FCCP-treated digitonin-permeabilyzed cells incubated in the presence of an excess of exogenous mitochondrial substrates. A crescent OCR was obtained when intact cells where incubated in medium contained the isolated metabolic substrates: glucose, pyruvate and glutamine. OCR by T98G and U-87MG cells was well coupled to ADP phosphorylation, as evidence by the amount of ATP produced for oxygen consumed, that was similar to that observed for isolated rat brain mitochondria. Glioma cells also displayed a high affinity for oxygen as indicated by the values of the partial pressure of oxygen where respiration is half maximal (p_{50}). In permeabilized cells, ADP-stimulated OCR was only about 50% of that obtained in the presence of FCCP, indicating that these cells have an important limitation of oxidative phosphorylation (OXPHOS) system relatively to the activity of the electron transport system (ETS). This characteristic was not modified when cells grew under low glucose. Flux control coefficient analyses have demonstrated that this impaired OXPHOS was mainly related to lower activities of both ATP synthase and adenine nucleotide translocator, but not to the phosphate carrier. **Conclusions:** Altogether, these data indicate that availability and metabolism of respiratory substrates and mitochondrial ETS are preserved in the highly glycolytic T98G and U-87MG glioma cells, nonetheless these cells possess a relative restrained OXPHOS capacity.

Keywords: cancer; glioma; mitochondrial energy metabolism; respiratory chain; oxidative phosphorylation; Warburg effect.

Financial support: *FAPESP, CNPq and CAPES.*