

HEPG2 CELLS ADAPT TO PHYSIOLOGICAL NORMOXIA BY THINNING MITOCHONDRIAL NETWORK TUBULES - 4Pi MICROSCOPY STUDY

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We have studied 72 hour adaptive responses of hepatocellular carcinoma HepG2 cells to 5% and 3.5% oxygen, representing normoxic and hypoxic environment of liver in vivo, respectively. Cells were cultivated either at 5 mM glucose (GLC5 cells, control), or at 25mM glucose (GLC25 cells, hyperglycemic, highly glycolytic), or with galactose with glutamine (OXPHOS cells, forced to oxidative phosphorylation). An instant hypoxic stress induced mitochondrial fission, from which cells recovered after several hours. A significant thinning of mitochondrial reticulum tubules, documented by a high (~100 nm) resolution 3-dimensional 4Pi microscopy, occurred with OXPHOS cells adapted to 3.5% to 5% oxygen. The insufficient fusion prevented formation of bulky tubules of mitochondrial reticulum or other potentially fused objects. Respiration decreased proportionally to lower oxygen under all conditions but state-4, indicating uncoupling. Thus a higher oxidative phosphorylation and lower superoxide production guarded by ready uncoupling is required to keep mitochondrial reticulum thin and continuous. This would be beneficial for spreading transcripts and/or expression products of mitochondrial DNA.

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