SUCCINATE REGULATES CELL GROWTH

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Succinate is an important citric acid cycle intermediate (Krebs, 1970). It was reported that a poor liver transplantation outcome can be due to a succinate cytochrome C reductase deficiency in the organ of the donnor (Zucker, 2005). This causes an increase of succinate concentration in blood and leads to multiorgan failure on the recipient. Recently, succinate was identified as the agonist of a cellular membrane G protein coupled receptor, GPR91 (He, 2004). Here, we investigate the presence of GPR91 on SkHep1, a hepatoma cell line. We also studied the effect of succinate on intracellular calcium signaling and gene transcription. GPR91 expression and localization were investigated by RT-PCR and immunofluorescence procedures. Calcium mobilization was visualized by confocal microscopy in Fluo-4/AM loaded cells. Gene transcription analysis was approached by Rapid Subtraction Hybridization (RaSH). We found that GPR91 is expressed in SkHep1 cells and it is present at the plasma membrane. Activation of GPR91 by succinate increases intracellular calcium signal. RaSH analysis indicated that succinate treatment induces genomic expression of two genes involved with cancer suppression: Cancer Metastasis Suppressor 1 and FAT tumor suppressor. Taken together, our results show that succinate induces intracellular calcium increase and trigger genomic expression of genes that regulate cell growth.

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