

審査の結果の要旨

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This study focused on metabolic remodeling of mitochondrial electron transport chain under hypoxia/hyponutrition and highly reactive oxygen species (hROS) generation following ischemia-reperfusion (IR). The following results have been obtained in the study:

1. This study established a specific, rapid, and reproducible assay system for succinate concentration. This method is unique in that it is a cycling assay and because of this, is more sensitive than conventional ones.
2. Using the assay, this study evaluated the intra- and extracellular succinate concentration of DLD-1, Panc-1, and HDF cells. Under 1% O₂/glc(-)gln(-), the quinol-fumarate reductase (QFR) activity of complex II (succinate:ubiquinone reductase) increases, becoming the major source of succinate accumulation.
3. By using respiratory chain (RC) inhibitors, two major sources of electrons leading to succinate accumulation under 1% O₂/glc(-)gln(-) were identified as complex I and dihydroorotate dehydrogenase (DHODH).
4. By combining the novel succinate determination assay and specific detection of hROS by Aminophenyl Fluorescein, this study also investigated the involvement of succinate onto hROS production and provided a direct evidence that mitochondrial complex II and possibly DHODH are the responsible hROS production site at 30 min following IR-mimicking condition and complex I has little role in hROS production..

These results suggest that under tumour microenvironment, “metabolic remodeling” occurs, in which electron flow alters from classical oxygen respiration to fumarate respiration, and that this remodeled metabolism becomes essential to support NADH re-oxidation as well as nucleotides biosynthesis. This study has also attained the profound insights into succinate-driven hROS production in cultured human cells.

Revealing the mechanism involved in succinate accumulation as well as succinate-mediated hROS production can provide leading drug candidates for treatment of a range of disorders including tumours and IR injury. Thus, this study has a major contribution and deserves the degree.