GENETICS AND GENODERMATOSES

PYRUVATE PROTECTS AGAINST CELLULAR SENESCENCE THROUGH THE CONTROL OF MITOCHONDRIAL AND LYSOSOMAL FUNCTION IN DERMAL FIBROBLASTS

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Introduction: In glucose metabolism, pyruvate is a key intermediate produced by glycolysis and can be converted to oxaloacetate via pyruvate carboxylase, to malate via malic enzyme, to acetyl-CoA via pyruvate dehydrogenase complex, or to lactate via lactate dehydrogenase. Although pyruvate was originally thought to be an additional energy source, or required for the generation of NAD+ using NADH to maintain redox balance.

Objective: Pyruvate, a key metabolite for numerous aspects of metabolism, has been used as general supplement in synthetic media. However, the physiological function of pyruvate underlying its protective role against cellular senescence under normal conditions has remained unknown.

Results: Pyruvate, which is imported through monocarboxylate transporters (MCTs) into the cells, inhibits senescence in dermal fibroblasts in both primary cell culture and 3D SEs model systems. NAD+, which is generated during the conversion of pyruvate to lactate by LDH-A, induces the deacetylation of SIRT1 targets such as PGC-1α, RelA, and v-ATPaseV0A1, and the deacetylation of SIRT6 target, histone H3K9ac. Under pyruvate deprivation conditions, the accumulation of acetylated PGC-1α induces the downregulation of UCP2, resulting in the elevation of the MMP, as well as the accumulation of acetylated v-ATPaseV0A1, and disruption of its interaction with LDH-B; this induces the dysregulation of lysosomal acidification, resulting in a series of events including mitophagy defects, the accumulation of abnormal mitochondria, an increase in mitochondrial ROS production, and the upregulation of SASP, which is induced by a combination of acetylated RelA and H3K9.

Conclusions: Our findings reveal a connection between pyruvate and mitochondrial dysfunction in the progression of senescence to our knowledge previously unreported. These results suggest that the pyruvate deprivation-induced senescence model can be used to study the connection between metabolism and senescence under normal conditions.