

## **EXPLORING METFORMIN ACTION ON THE REGULATION OF CANCER CELL PROLIFERATION**

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The increasing incidence of various cancer types leads to the development of specific therapies focusing on altered metabolism of cancer cells. Rapid growth and fast proliferation of some tumors require specific adaptations of cellular metabolism comprising high rates of glucose utilization and subsequent NADH re-oxidation. To sustain high glycolytic rate, many cancer cells depend on functional mitochondrial respiration, in which glycerophosphate-(GP)-shuttle connects mitochondrial and cytosolic transduction pathways. Mitochondrial FAD-dependent glycerol-3-phosphate dehydrogenase (mGPDH) is a rate-limiting component of GP shuttle; hence, its activity may be crucial for efficient tumor cell proliferation.

In this work, we focused on the action of metformin (MF) on tumor cell proliferation as MF has recently been demonstrated to act as mGPDH inhibitor. For this purpose, we identified several cancer cell lines of metastatic origin with high mGPDH content and activity and treated them with MF. We observed decrease in cell proliferation, yet solely associated with suprapharmacological levels of MF and therefore this could be explained by apoptosis/necrosis induction than by any specific MF action. However, as epidemiological evidence from type II diabetes patients on MF treatment clearly points to reduced cancer risk in this cohort, we propose an indirect modulatory mechanism to be causative for the antitumorigenic potential of MF rather than direct enzyme inhibition and subsequent reduced cell proliferation. We examined two different MF actions: (1) how mitochondrial substrate utilization underlies cancer cell sensitivity to MF, (2) its effect on the components of immune system. We showed that MF affected cell proliferation in time dependent manner in nutrient restricted environment. Concerning MF action on immune system, we identified its immunomodulatory properties as it altered immunophenotype together with respiratory and metabolic profiles of various immune populations. Most prominently, MF interfered with the generation of monocyte-derived dendritic cells. Altogether, our results might be an asset for anticancer therapies.

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