ANTICANCER EFFECTS OF METFORMIN INVOLVE SUPPRESSION OF CELLULAR NADH SINKS AND REDUCTIVE STRESS.

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Metformin is a biguanidine drug used for the treatment of type II diabetes. Antidiabetic effects of metformin have largely been attributed to the ability of the drug to activate AMP-activated kinase (AMPK) that stimulates insulin-independent glucose uptake. Metformin has also been receiving increasing attention as a potential therapeutic option for various types of cancer due to its significant pro-apoptotic effects eliminating cancer cells in culture and suppressing tumor progression in mice. Epidemiologic data largely obtained from diabetic patients corroborate the idea that metformin may be beneficial for the prevention of cancer onset. As in the case of diabetes, the anticancer effects of metformin have also largely been attributed to the activation of AMPK. However, has been recently confronted by a number of studies that showed essential roles of AMPK in promoting tumor progression. Consistent with these studies, we now show that AMPK-deficient cells (shAMPK/MCF7) are more sensitive to metformin-induced apoptosis than AMPK competent MCF7 cells. This result indicated that AMPK is dispensable for metformin-induced killing of cancer cells. Moreover, we showed that in AMPK competent cells, pyruvate supplementation reverses cell killing by metformin via increasing [NAD⁺] and promoting ATP generation. In shAMPK/MCF7 cells, pyruvate supplementation failed to restore NAD⁺ and ATP production being ineffective against metformin-induced cell death. These cells, however, could utilize an alternative carbonyl (acetoacetate) produced by the ketogenic pathway from acetylCoA to serve as an electron acceptor for NADH. Collectively, our findings indicate the following: (i) Metformin killing of cancer cells is independent of AMPK (ii) The anticancer effects of metformin are largely modulated by the availability of specific electron accepting carbonyls in the microenvironment (iii) under conditions of inhibited electron transfer chain, AMPK regulates mechanisms of carbonyl disposition by defining specific electron acceptors that regenerate NAD⁺ thereby suppressing NADH overload and reductive stress.