DIFFERENTIAL ANTI-CANCER EFFECTS OF METFORMIN AGAINST RENAL CELL CARCINOMA

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Renal cell carcinoma accounts for 3-5% of all cancers among US adults. Mutation of Von-Hippel Lindau (VHL) tumor suppressor gene and the resultant overexpression of hypoxia-inducible factor-1 alpha protein trigger cell proliferation, epithelial-mesenchymal transition (EMT), deregulated autophagy, and angiogenesis, ultimately resulting in RCC progression and metastasis. In this study, we investigated the response of two human RCC cell lines Caki-1 and Caki-2, which express wild-type and mutated VHL respectively, to metformin (an anti-diabetic drug). Our findings demonstrate a differential response between the two RCC cell lines studied, with Caki-2 cells being ten-times more sensitive to metformin’s cytotoxic and anti-proliferative effects compared to Caki-1 cells, i.e., 20 mM vs. 2 mM metformin to produce 18% cell death, and 50 mM vs. 5 mM metformin to induce a significant cell cycle arrest at G0/G1 phase in Caki-1 and Caki-2 cells respectively. In contrast, the Caki-1 cells were more sensitive to metformin-induced suppression of EMT (evidenced by a reduction in the expression of alpha-SMA, an EMT marker) as compared to Caki-2 cells, i.e., 5 mM vs. 10 mM metformin required to produce 36% reduction in α-SMA expression in Caki-1 and Caki-2 cells respectively. Intriguingly, both cells were equally sensitive to metformin-induced inhibition of autophagy - marked by reduced expression of LC3II, a marker of autophagy. Together, our study unveils the therapeutic potential of metformin to inhibit the progression of RCC in vitro. Further studies in vivo and humans are required to ascertain the therapeutic efficacy of metformin against RCC.

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