

Induction of altered cellular response to oxidative stress in HT29 colon cancer cells treated with Metformin

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Accumulating evidences suggest that Metformin, a biguanide class of anti-diabetic drugs, possesses anti-cancer properties (1). In a number of preclinical and clinical studies, Metformin reduced proliferation, induced apoptosis, caused cell cycle arrest, and reduced incidence and growth of tumors (2). HT-29 is a human colorectal adenocarcinoma cell line with epithelial morphology and represents a xenograft tumor model for colorectal cancer. Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor that controls the expression of a large pool of antioxidant and cytoprotective genes, regulating the cellular response to oxidative and electrophilic stress. Evidences have suggested that mutations in Nrf2 are common in cancer cells, which could help tumor cells surviving, and might be associated with poor survival of cancer patients. In our study the HT29 cells were treated with graded concentrations of Metformin for 24, 48 and 72 hours. We performed immunofluorescence experiments by means of confocal microscopy, western blot and cytofluorimetric analysis to evaluate a panel of factors involved in apoptotic/autophagic processes and oxidative stress response. Our results demonstrate that Metformin exerts growth inhibitory effects on cultured HT29 cells by increasing apoptosis and autophagy; moreover, it affects the survival of cultured cells inhibiting the transcriptional activation of both Nrf2 and NF- κ B. The effects of Metformin on HT29 cells were dose dependent as well as time dependent, because it has been showed a significant change in the parameters analyzed after 72 hs versus 24 hs of treatment. Therefore, constitutive activation or augmented signaling of the Nrf2 pathway might be decisive for cell fate during tumorigenesis and could affect the response to chemotherapy.

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References

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Keywords

Metformin; tumorigenesis; human HT-29; oxidative stress.