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Effects of metformin in the breast tumor development in obese rats: Mechanisms involved

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Epidemiological studies have associated obesity with a wide variety of cancers such as breast and colon cancer. Insulin resistance, hyperinsulinemia, hyperglycemia and inflammation have been proposed as the mechanisms by which obesity induces or promotes tumorigenesis. Metformin, an anti-diabetic drug commonly prescribed to treat type 2 diabetes, has recently received attention as a potentially useful therapeutic agent for reducing cancer development. It is reported to not only have a direct antitumoral effect, but also to act indirectly to improve insulin sensitivity, decreases hyperinsulinemia, and consequently attenuate tumor proliferation. Then, the objective of the present work was to analyze the mechanisms associated with the higher development of tumor in obesity and analyze the mechanisms by which metformin reduces tumor size. Obesity was induced in newborn male Wistar rats by subcutaneous injection of 400 mg/kg body weight monosodium glutamate (MSG) (obese) or saline (control) at 2, 3, 4, 5 and 6 days of age. After 16 weeks, 1x107 Walker-256 tumor cells, a rat breast carcinosarcoma cell lines, were subcutaneously injected in the right flank of the rats and concomitantly were treated with metformin, 300 mg/kg body weight, via gavage, for 15 days. Following this treatment, the rats were divided into 4 groups: control tumor (CT), control tumor metformin (CTM), obese tumor (OT) and obese tumor metformin (OTM). The effect of metformin on tumor development was assessed at the 18th week. Tumor development was higher in OT rats compared with CT rats which correlated with reduced life span in OT compared with CT rats. The mechanisms associated with higher development of tumor in obesity are insulin resistance, activation of insulin-IR-ERK1/2 pathway and anti-apoptotic action, via Bcl-2. Metformin reduced the tumor development in OT rats and prolonged the life span of the rats. Metformin increased the mRNA expression of cell cycle regulators pRb and p27. Furthermore, metformin increased AMPK and FOXO3a activities, and decreased p-ERK1/2 expression in CTM and OTM groups. In order to further explore the molecular mechanism of the antiproliferative role of metformin, breast cancer MCF-7 cells were treated with metformin for 24, 48 and 72 hours. Results indicated that the antiproliferative effect of metformin was both time- and dose-dependent. This effect was associated with an increase in oxidative stress, apoptosis, necrosis and cell cycle arrest in G0-G1 phase as measured by flow cytometry. Metformin also increased mRNA expression of FOXO3a, p27, Bax and decreased the mRNA expression of cyclin D1 and Bcl-2 as well as decreased the Bcl-2 protein expression. Furthermore, metformin increased AMPK and FOXO3a activities. Moreover, the combination of metformin+H2O2 exhibited an even stronger antiproliferative effect as compared to the individual treatments. In conclusion, we have demonstrated that obesity has an important role in tumor development, increasing the tumor size and reducing the life span of the rats. We have also demonstrated that metformin was effective in controlling tumor development and prolonging the survival; effects associated with AMPK and FOXO3a. Financial support: FAPESP and CNPq (Brazil), NSERC-RCD and NOSM (Canada).

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