ANTITUMOR EFFECTS OF CURCUMIN ANALOGS IN TRIPLE NEGATIVE BREAST CANCER (TNBC) CELL LINES

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Introduction: Many research groups considered curcumin as a very good lead compound to design a large variety of analogs as potential new antitumor drugs, more effective and able to overcame drug resistance with respect to conventional ones. We analysed antitumor effects of three curcumin derivatives, (1E,6E)-1-(4-hydroxy-3-methoxyphenyl)-7-(3-methoxy-4-propargyloxyphenyl)hepta-1,6-diene-3,5-dione (1), (1E,6E)-1,7-bis(3-methoxy-4-propargyloxyphenyl)hepta-1,6-diene-3,5-dione (2) and 4-phenylsulfanyl-(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (3), on two triple negative breast cancer (TNBC) cell lines, SUM 149and MDA-MB-231. TNBCs are highly aggressive with poor prognosis and often resistant to cytotoxic chemotherapy. Therapeutic choice is limited by the lack of expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor (Her-2) and by high molecular heterogeneity. Moreover the aberrant activation of nuclear factor NF-κB signalling is a frequent characteristic of TNBCs.

Methods: The compounds 1and 2were synthesized following literature procedure, while compound 3was obtained by reaction of curcumin with benzenesulfenic acid, generated in situ from the suitable precursor, following an original synthetic procedure. The effects of compounds on cell viability and apoptosis were examined by MTS assay and flow cytometry analysis, respectively. NF-κB activation was evaluated by TransAM assay, while expression of different factors by Western Blot analysis.

Results: In the two triple negative breast cancer cell lines, the analogs showed increased cytotoxic effects and an higher or at least equivalent cell death induction than curcumin, proving that small modifications can give access to compounds exhibiting antitumor activities superior to those of curcumin. In the two cell models, the addition of N-acetyl-L-cysteine (NAC) reduced cytotoxic activity of compounds 1and 2, but not of 3, thus the antitumor effects seem to be due to pro-oxidant mechanisms, at least for 1and 2. In both cell lines all derivatives showed ability to inhibit NF-κB DNA-binding activity at different times of administration, in particular in SUM 149compound 3exhibited stronger reduction than curcumin after 24h of treatment, while in MDA-MB-231compound 1showed a greater effect than curcumin after 8h of treatment. In addition, the compound 3in SUM 149cells and the compound 1in MDA-MB-231caused a decreased expression of some anti-apoptotic factors and NF-κB targets.

Conclusion: Finally, our data confirmed once again that curcumin may represent an important basis for the development of more effective analogs that appear new anticancer agents even in tumors difficult to treat as TNBCs.