OC-19

MODIFIED DOXORUBICINS: "GASEOUS APPROACH" TO OVERCOME CARDIOTOXICITY AND MULTIDRUG RESISTANCE

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Doxorubicin (DOXO) is one of the most effective antineoplastic agents in clinical practice. It is used as single agent or in combination with other anticancer drugs in treating of hematological cancers, solid tumors, lymphomas, and sarcomas.[1] Its use is limited by acute and chronic side effects, in particular by its cardiotoxicity and by the rapid development of resistance to it.[2,3] As part of a program aimed at developing new DOXO derivatives endowed with reduced cardiotoxicity, while active against DOXO-resistant tumor cells, a series of H_2S-releasing DOXOs (H_2S-DOXOs) were obtained by combining DOXO with appropriate H_2S donor substructures (Fugure 1). Indeed H_2S exhibits strong cytoprotective effects through a combination of antioxidant and antiapoptotic signals.[4] A number of recent reports show that sodium hydrosulfide, which at physiological pH is in equilibrium with H_2S, attenuates doxorubicin-induced cardiotoxicity in H9c2 embryonic rat cardiac cells, by inhibiting endoplasmatic reticulum (ER) stress and oxidative stress. Inhibition of the p38 MAPK pathway, activated by DOXO, seems to be another important mechanism underlying this protection. On the basis of this rationale, H_2S-DOXOs might be expected to be chimeras endowed with improved biochemical profiles than the antibiotic lead.

The resulting compounds were studied on H9c2 cardiomyocytes and in DOXO-sensitive U-2OS osteosarcoma cells, as well as in related cell variants with increasing degrees of DOXO-resistance. Differently from DOXO, most of the products were not toxic at 5 µM concentration on H9c2 cells. A few of them triggered high activity on the cancer cells. In particular two compounds emerged as the most interesting members of the series. The capacity of the most interesting H_2S-DOXO to impair Pgp transporter and an hypothesis of its mechanism of antitumor activity were investigated.

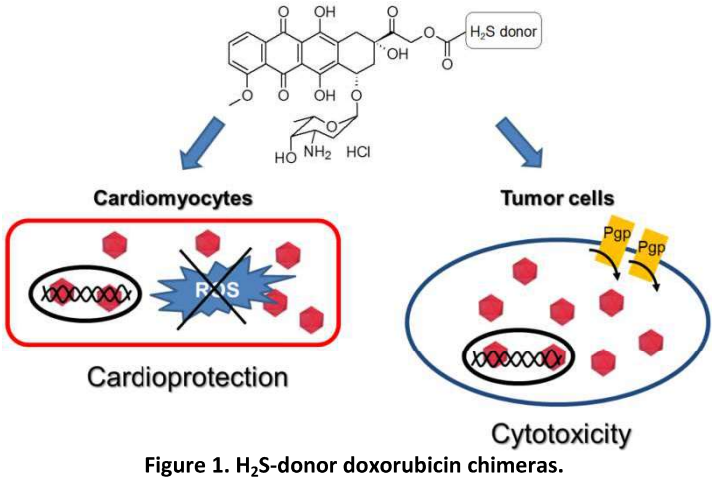

Figure 1. H_2S-donor doxorubicin chimeras.

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