Lipoxygenase inhibitors suppress proliferation of G5:113 fibrosarcoma cells in vitro but they have no anticancer activity in vivo*

Z. Hoferova¹, P. Fedorocko², M. Hofer¹, J. Hofmanova¹, A. Kozubík¹, V. Eliášová²

¹Institute of Biophysics, Academy of Sciences of the Czech Republic, Brno, Czech Republic, e-mail: zhofer@ibp.cz; ²Department of Cellular and Molecular Biology, Faculty of Sciences, Safář University, Košice, Slovak Republic

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Nordihydroguaiaretic acid (NDGA) and esculetin, both nonspecific inhibitors of lipoxygenases (LOX), were found to suppress expressively the in vitro proliferation of fibrosarcoma cells G5:113 in concentrations ranging from 10 to 50 μM. Subsequent flow-cytometric analysis of the cell cycle showed that both these drugs significantly decreased the percentage proportion of cells in the G₀/G₁-phase and simultaneously increased significantly this proportion in the S-phase. No apoptosis was detected in the whole range of concentrations studied, from 2.5 to 50 mM.

On the contrary, in experiments in vivo, neither NDGA nor esculetin had any curative effect if they were repeatedly injected intraperitoneally (i.p.) into mice bearing tumors growing from subcutaneously (s.c.) transplanted G5:113 cells. Pretreatment of the fibrosarcoma cells with NDGA or esculetin in vitro preceding their s.c. transplantation into mice did not result in suppression of the tumor growth, either. Finally, if G5:113 cells were injected intravenously and the mice were subsequently treated repeatedly with i.p. injections of NDGA, decreased survival and increased number of surface lung metastases were observed in the NDGA-treated group. Thus the suppressive action of inhibitors of LOX on the growth of fibrosarcoma cells in vitro was not reflected in their anti-tumor effects in vivo.

Key words: fibrosarcoma, lipoxygenase inhibitors.

The role of arachidonic acid (AA) metabolism in modulation of cancer development has been examined by numerous investigators using various inhibitors of AA metabolism. The attention has been focused on inhibition of metabolites produced by cyclooxygenases (COX) obtained by administration of various nonsteroidal anti-inflammatory drugs (NSAIDs). In animal experiments and clinical trials, suppression of the development and progression of solid tumors in vivo both in animals and in humans were found [see e.g. 7, 14, 30].

Once released, AA is converted by catalytic action of 5-, 12- or 15-lipoxygenases (LOX) into the corresponding hydroperoxyicosatetraenoic acids (HPETEs) which are further metabolized either to hydroxyeicosatetraenoic acids (HETEs) and leukotrienes or lipoxins through additional sequential reactions. Particularly the products of 5- and 12-LOX may play important roles in tumor promotion, progression and metastatic disease [33]. It was shown that 5-LOX was universally expressed in many cancer cell lines of colon, lung, breast and prostate [2, 11]. Inhibition of 5-LOX reduced the proliferation while the addition of 5-HETE stimulated the growth of cultured lung cancer cells [2]. The ability of tumor cells to generate 12-HETE is positively correlated with their metastatic potential. Extensive studies by Honn’s group have demonstrated the involvement of 12-LOX products in multiple steps of the metastatic cascade encompassing tumor cell-vasculature interactions, tumor cell motility and proliferation, proteolysis (collagenase IV release from tumor cells), intravasation/extravasation and angiogenesis [12]. A novel approach for cancer chemoprevention could also involve LOX modulators, i.e., agents that can induce the anticarcinogenic 15-LOX [32] and/or inhibit the procarcinogenic 5- and 12-LOX, thereby shifting the

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