NOVEL HIF1α INHIBITORS SUPPRESS CANCER CELL GROWTH AND CIRCUMVENT MULTIDRUG RESISTANCE

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Introduction Hypoxia is one of the causes of the resistance of tumours to various therapeutic agents. Most solid tumours contain hypoxic regions and adapt to low levels of oxygen by producing hypoxia-activated molecules, among which HIF-1α (Hypoxia-Inducible Factor 1-alpha) is key. HIF-1α is upregulated in many types of solid cancers and contributes to tumour progression by stimulation of VEGF-A expression and subsequent neoangiogenesis. The goal of the study was to synthesise a series of novel hypoxic cytotoxins and to evaluate their anticancer potencies.

Material and methods A series of 3-aryl/heteroarylquinoxaline-2-carbonitrile 1,4-dioxides was synthesised by Beirut reaction. Cancer cell lines were purchased from ATCC. The cytotoxic activity of quinoxaline 1,4-dioxides was evaluated in normoxia (21%O2) and hypoxia (1%O2). The cytotoxicity was assessed by MTT test (72 hour growth with compounds). HIF-1α and p53 activation was assessed by reporter analysis. The presence of ROS in MDA-MB-231 breast cancer cells was detected using the fluorescent probe 2',7'-dichlorofluorescin diacetate.

Results and discussions Lead compounds in series quinoxaline 1,4-dioxides demonstrated better cytotoxicity and comparable hypoxia selectivity for human breast adenocarcinoma cell lines MCF-7 and MDA-MB-231 than the reference agent tirapazamine. In contrast to reference antibiotic doxorubicin, quinoxaline 1,4-dioxides inhibited hypoxia-mediated HIF-1α activation and showed potent cytotoxicity against multidrug resistant human chronic myeloid leukaemia K562/4 cells with overexpression P-glycoprotein (Pgp). Selected compound LCTA-2809 (6,7-dichloro-3-phenylquinoxaline-2-carbonitrile 1,4-dioxide) inhibited of cancer cell growth through p53-independent mechanisms. Compound LCTA-2809 showed no effects on p53-dependant luciferase activity, when doxorubicin revealed high potency to activate p53-dependant reporter in MCF-7 cells. Our results revealed that compound LCTA-2809 sensitised MCF-7 cells to bignanide metformin in hypoxia. Short-term treatment with LCTA-2809 resulted in the fast increase of ROS accumulation in cancer cells.

Conclusion HIF-1α inhibitor LCTA-2809 can be considered as the lead compound for further anticancer drug design, evaluation, and development of new potent antitumor agents. The biology experiments of the research were supported by RSF 14-15-00362.

NOVEL DRUG DISCOVERY APPROACHES FOR CANCER WITH THE INSPIRATION OF A NATURAL PRODUCT – METHYL JASMONATE

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Introduction Cancer is one of the well-known illnesses leading to death. Clinical validations prove that protein kinases are an attractive class of therapeutic drug targets for cancer as demonstrated with the recent approval of six protein kinase inhibitors. The Warburg effect describes the particular reliance of cancer cells on glycolysis for energy. Increased glycolysis and acid resistance have been postulated to be an essential part of carcinogenesis, conferring a significant growth advantage as well as promoting typical tumour progression. Targeting accelerated glycolysis in cancer cells is a new promising modality for treatment of cancer. Inhibition of glycolysis can be done without significant side effects, and such treatment will be additive to most known cancer therapies.

One way to inhibit the metabolism of cancer cells is to inhibit Hexokinase 2 (HK-2) enzyme. HK-2 has been studied in the field of cancer metabolism and hopeful results obtained. It has been also confirmed that HK-2 enzyme is expressed 10–15 times more in cancer cells than normal cells. Inhibition of HK-2 enzyme will prevent cancer cells from nutrition and it is expected that speeding of cancer cells will presumably stop tumour growth.

Material and methods Recent studies show that Methyl Jasmonate reveals promising results for treatment of cancer as a HK-2 inhibitor. cis-Jasmonate, Jasmonic acid and Methyl jasmonate are cyclopentanones that are fatty acid derivatives. Jasmonates are plant stress hormones which exhibit abnormal anti-cancer activity. Jasmonates induced suppression of cell proliferation and death in a variety of cancer cell lines and cytotoxicity to cervical cancer cells with almost no effect on normal primary human keratinocytes. As a result of our research, although methyl jasmonate is long-known natural product, it has not well-studied as an anti cancer agent.

Results and discussions In our research laboratory, we designed and synthesised handful of novel methyl jasmonate analogues. We will highlight the biological activity results of those novel analogues as anti-cancer agents as well as their toxicologic profiles will be highlighted.

Conclusion As a result of this study, we have identified several novel methyl jasmonate analogues that are much more potent in biological assays. Based on the synthetic feasibility and freedom of operation of methyl jasmonate molecule, additional druggable analogues are also being investigated in our research.

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ESTIMATION OF ANTITUMOR ACTIVITY OF AMINO DERIVATIVES OF QUINOXALINE-2-CARBONITRILE 1,4-DIOXIDE

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Introduction Tumour hypoxia and its key mediator the HIF-1α contributes to tumour aggressiveness and responsible for major distinguishing features of cancer including metastasis, invasion