Journal of
Cellular and Molecular Pharmacology

Commentary Open Access

Mechanism of Gemcitabine - Cellular Pharmacology

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Commentary

Gemcitabine (2', 2'-difluoro 2'-deoxycytidine, dFdC) is an analogue of cytosine arabinoside (Ara-C) from which it differs structurally due to its fluorine substituents on position 2' of the furanose ring. It has been the most essential cytidine analogue to be developed since Ara-C, showing distinctive pharmacological properties and a broad spectrum of antitumor activity. Originally investigated as an antiviral agent, it was then developed as an anticancer drug on the basis of its impressive in vitro and in vivo anti-tumoral activity. The evidence of the efficacy of gemcitabine to inhibit the increase of human neoplasms was obtained in a vast range of solid and haematological cancers cell lines, as well as in invivo murine solid tumors and human tumor xenografts in nude mice. Consequently gemcitabine was studied in a variety of tumors in which vast significant clinical activity has been reported. Today gemcitabine is indicated as a single agent in the treatment of sufferers with metastatic pancreatic cancers and in combination chemotherapy in non-small cell lung cancer, bladder cancer and breast cancer. Gemcitabine has additionally been effectively used in different tumors such as ovarian cancer, mesothelioma and head and neck cancers.

Like Ara-C, gemcitabine is a prodrug which requires cellular uptake and intracellular phosphorylation. Inside the cell, gemcitabine is phosphorylated to gemcitabine monophosphate (dFdCMP) by deoxycytidine kinase (dCK), which is then transformed to gemcitabine di- and triphosphate (dFdCDP and dFdCTP, respectively). These are the active drug metabolites. In contrast to Ara-C, gemcitabine has more intracellular targets. Its antiproliferative activity is believed to be dependent mainly on several inhibitory actions of DNA synthesis.

dFdCTP is an inhibitor of DNA polymerase and is integrated into DNA. After incorporation of one extra nucleotide by using DNA polymerase into the DNA chain, it leads to termination of chain elongation. The non-terminal position of dFdCTP in the DNA chain prevents detection and by DNA repair enzymes (masked chain termination). These molecular events are critical to gemcitabine-induced apoptosis. A metabolite of dFdC, most likely dFdCTP, is also known to incorporate into RNA. The impact of this RNA incorporation on cell function is, however, unclear.

As with Ara-C, the main mechanism of action of gemcitabine is a potent inhibition of DNA synthesis. The killing effects of gemcitabine are not restricted to the S phase of the cell cycle and the drug is equally effective against confluent cells and cells in log-phase growth. Important variations exist between Ara-C and gemcitabine concerning the mode of incorporation into DNA, existence of additional sites of action and consequent kinetic properties of cell growth inhibition and spectrum of activity.

The potent cytotoxic activity of gemcitabine is the result of additional action on DNA synthesis: dFdCTP competes with deoxycytidine triphosphate (dCTP) as a weak inhibitor of DNA polymerase. dFdCTP is integrated into DNA and, after the incorporation of one more nucleotide, leads to DNA polymerization termination and single strand breakage. This 'extra' nucleotide is important in hiding the dFdCTP from DNA repair enzymes, because incorporation of gemcitabine into DNA apears to be resistant to the normal mechanisms of DNA repairs.

It is still unclear by which downstream molecular pathway gemcitabine incorporation into DNA leads to cell death. Apoptosis-regulating genes, such as p53, bcl-2, bcl-xLBAX, regulate cancers cell sensitivity/resistance to gemcitabine. In some solid human tumor cell lines gemcitabine induces apoptosis by activation of a number of caspases (e.g. caspase 8 and caspase 3), key factors of the apoptotic pathways. This suggests a vital role of caspase activation in gemcitabine sensitivity/resistance.

Gemcitabine has acquired a relevant role in the treatment of several solid tumors. Despite its success, the fact that the antitumor activity and toxicity of gemcitabine varies from one person to another and the improvement of drug resistance remain important causes of low response rates and lack of efficacy in relapsed tumors as well as unpredictable severe toxic effects.

These phenomena are believed to be related to variations in drug intracellular metabolite levels and activities of drug transporters, drug metabolizing enzymes, target enzymes and enzymes involved in programmed cell death between different normal and tumour cell types and individuals. Knowledge of gemcitabine intracellular pharmacology is thus potentially relevant to a more comprehensive understanding of the mechanisms of sensitivity/resistance and toxicity to this drug, and will assist in the development of therapeutic strategies aimed at improving treatment efficacy while reducing drug toxicity. Recently, clinical pharmacogenomics and pharmacokinetic studies have provided initial confirmation of the role of differential expression and polymorphisms of genes whose protein products are involved in gemcitabine transport, metabolism and action in drug response and toxicity.

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Received December 13, 2021; **Accepted** December 27, 2021; **Published** January 03, 2022

Citation: Krishna S (2021) Mechanism of Gemcitabine - Cellular Pharmacology. J Cell Mol Pharmacol 5: 110.