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REVIEW ARTICLE

Promising molecular mechanisms responsible for gemcitabine resistance in cancer

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Abstract Gemcitabine is the first-line treatment for pancreatic ductual adenocarcinoma (PDAC) as well as acts against a wide range of other solid tumors. Patients usually have a good initial response to gemcitabine-based chemotherapy but would eventually develop resistance. To improve survival and prognosis of cancer patients, better understanding of the mechanisms responsible for gemcitabine resistance and discovery of new therapeutic strategies are in great need. Amounting evidence indicate that the developmental pathways, such as Hedgehog (Hh), Wnt and Notch, become reactivated in gemcitabine-resistant cancer cells. Thus, the strategies for targeting these pathways may sensitize cancer cells to gemcitabine treatment. In this review, we will summarize recent development in this area of research and discuss strategies to overcome gemcitabine resistance. Given the cross-talk between these three developmental signaling pathways, designing clinical trials using a cocktail of inhibitory agents targeting all these pathways may be more effective. Ultimately, our hope is that targeting these developmental pathways may be an effective way to improve the gemcitabine treatment outcome in cancer patients.

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Introduction

Gemcitabine (2′,2′-difluoro-2′-deoxycytidine; dFdC)[1] is a novel deoxycytidine analogue. Despite of some similarities with other nucleoside analogues such as cytosine arabinoside (AraC), gemcitabine has several unique properties and specific spectrum of activity.[2,3] The cytotoxic lesions caused by gemcitabine include killing cells with active DNA synthesis (S phase) and blocking cell cycle progression at the G1/S phase boundary.[4] Gemcitabine was originally used for its antiviral effects but is now widely used as an anti-cancer chemotherapeutic agent. Gemcitabine is recommended as a single agent for first-line chemotherapy for patients with advanced pancreatic cancer.[5] It is also used for chemotherapy for patients with non-small cell lung cancer,[6] breast cancer,[7] bladder cancer[8] and ovarian cancer.[9]

Patients usually have a good initial response to gemcitabine-based chemotherapy but develop resistance by time. Gemcitabine resistance can be either intrinsic or acquired. Resistance can result from molecular and cellular changes, including nucleotide metabolism enzymes, inactivation of the apoptosis pathway, high expression of drug efflux pumps, activation of the cancer stem cells or epithelial-to-mesenchymal transition (EMT) pathway, up- or down-regulated expression of microRNA (miRNA) (Fig. 1). It has been demonstrated that pathways such as Hedgehog (Hh), Wnt and Notch, which regulate embryonic development and somatic stem cells (SCs), can be reactivated in gemcitabine resistance cancer cells (Fig. 2). Herein, we will describe recent advances towards targeting these pathways with a goal to overcome gemcitabine resistance.

Gemcitabine metabolism and mechanism of action

Gemcitabine is transported into cells by sodium-dependent (concentrative nucleoside transporter hCNTs) and sodium-independent (equilibrative nucleoside transporter hENTs) mechanisms.[10,11] Once inside the cell, gemcitabine undergoes a series of phosphorylation by deoxycytidine kinase (dCK) to the monophosphate (dFdCMP) and then by pyrimidine nucleoside monophosphate kinase (UMP—CMP kinase) to give gemcitabine diphosphate (dFdCDP), resulting in formation of gemcitabine triphosphate (dFdCTP) mediated by nucleoside diphosphate kinase (NDPK).[12] The first phosphorylation by dCK is considered the rate-limiting step for dFdCDP and dFdCTP production.

Gemcitabine can get inactivated through deamination by cytidine deaminase (CDA), and when in the monophosphate form by deoxycytidylate deaminase (dCTD). Gemcitabine may also become inactivated by dephosphorylation of the monophosphate form by 5′-nucleotidases (5′-NTs), converting nucleotides back to nucleosides. On the other hand, gemcitabine exhibits a unique property called self-potentiation to enhance its activation. The diphosphate form (dFdCDP) inhibits ribonucleotide reductase M1 or M2 (RRM1/RRM2) that convert CDP to dCDP, leading to depletion of dCTP pools and facilitating incorporation of dFdCTP into DNA.[13]

Known mechanisms of gemcitabine resistance

One mechanism responsible for gemcitabine resistance is the dysregulation of the proteins participating in gemcitabine metabolism pathways, including deficiency of hENT1,

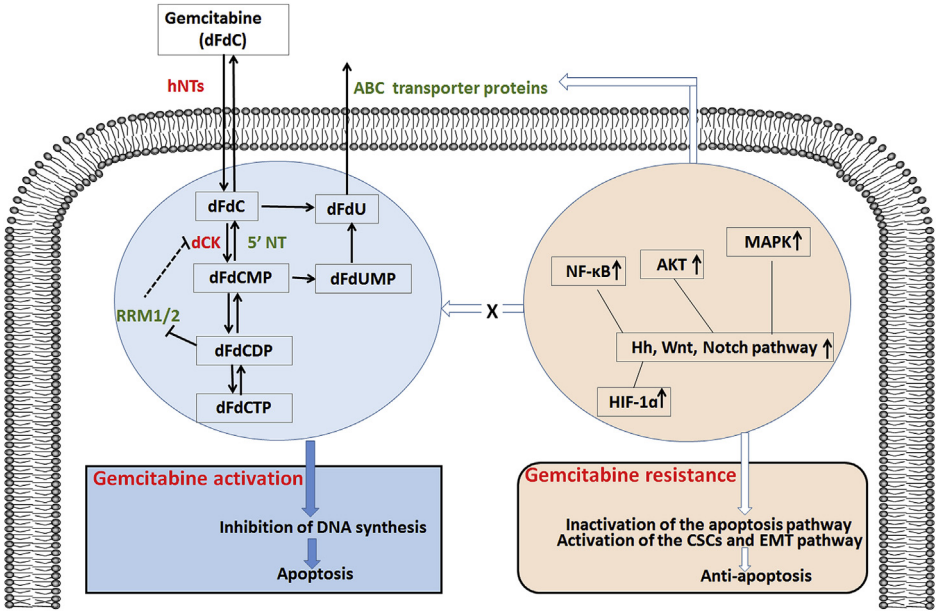

Fig. 1 A diagram of gemcitabine metabolism and proposed mechanisms of gemcitabine resistance. Gemcitabine (dFdC) is a pro-drug that requires cellular uptake and serial phosphorylation to become pharmacologically active. Gemcitabine can interrupt DNA synthesis and then induce cancer cells apoptosis. Gemcitabine resistance can be either intrinsic or acquired. Resistance can result from molecular and cellular changes, including nucleotide metabolism enzymes, apoptosis pathway, ABC transporter proteins, activation of the CSCs and EMT pathway.