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Failure of Pancreatic Cancer Chemotherapy: Consequences of Drug Resistance Mechanisms

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1. Introduction

Pancreatic cancer is one of the most lethal forms of cancer and it is estimated that there will be about 44,000 new cases in US in the year 2011. With 37,600 estimated deaths in 2011, pancreatic cancer is the fourth leading cause of cancer related deaths in US (*American Cancer Society, 2011*). In spite of numerous efforts, the 5-year survival rate for pancreatic cancer has not improved much for the last few decades. The suggested reasons for low survival among the pancreatic cancer patients include late disease diagnosis, highly invasive and metastatic nature, lack of effective therapies, and acquisition of resistant characteristics (*American cancer Society 2007; Moore, et al., 2003; NIH 2007*). Only two drugs – gemcitabine (GEM) and 5-fluorouracil (5FU) – have been shown to improve the survival of patients consistently. 5FU was the first drug to be approved as adjuvant therapy for pancreatic cancer (*Kalser and Ellenberg, 1985; Moertel, et al., 1981*). Since then, GEM has been used as the first line chemotherapeutic drug for pancreatic cancer. However, GEM treatment does not always provide extended survival benefits. A study found that in post-operative patients, GEM treatment increased the survival by merely 6 months (*Shore, et al., 2003*). 5FU is also widely used as an adjuvant and neoadjuvant chemotherapeutic agent to treat pancreatic cancers (*Ahlgren, 1996; Blaszkowsky, 1998; Snady, et al., 2000*).

Although the cell death mechanisms induced by GEM and 5FU are well understood, their efficacy is limited due to the acquisition of drug-resistant characteristics by the cancer cells. Various molecular mechanisms have been suggested to play a role in development of resistance against these drugs. Upregulation of Akt (protein kinase B), NFκB, MDR (p-glycoprotein) and hypoxia have been shown to impart resistance against GEM (*Bergman, et al., 2002; Galmarini, et al., 2002; Garcia-Manteiga, et al., 2003; Nakano, et al., 2007; Yokoi and Fidler, 2004*). Similarly, modulation of thymidylate synthetase (TS), dihydropyrimidine dehydrogenase (DPDY), MAPK, p53 and *src* imparts 5FU resistant characteristics to

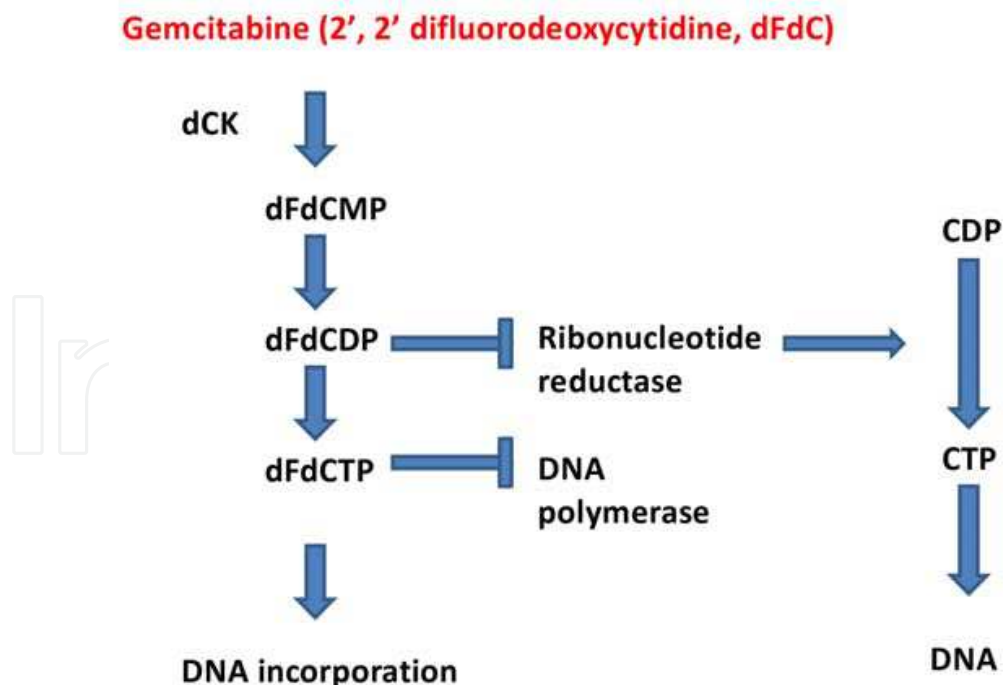
pancreatic cancer cells (Eisold, et al., 2004; Kang and Saif, 2008; Zhang, et al., 2008; Zhao, et al., 2006b). Epidermal growth factor receptor (EGFR) is a mitogenic receptor which has also been shown to provide cancer cells with proliferative and anti-apoptotic advantage (Arteaga, 2001; Citri and Yarden, 2006). EGFR is found to be upregulated in pancreatic cancer patients' tumors and the levels of EGFR correlate with aggressiveness and poor prognosis of the disease (Yamanaka, et al., 1993).

2. Pancreatic cancer chemotherapy

In spite of numerous efforts, the 5-year survival rate for pancreatic cancer has not improved much for last few decades. One reason contributing to this is the lack of chemotherapeutic agents which would effectively improve the survival of patients (American Cancer Society, 2011; Moore, et al., 2003).

2.1 Gemcitabine

Gemcitabine (2', 2'- difluorodeoxycytidine) is a difluoro analog of deoxycytidine and is the first line chemotherapeutic agent used in the treatment of pancreatic cancer cells. In 1997, a randomized trial found gemcitabine to have better clinical benefit response of 23.8% to 4.8% when compared to 5-fluorouracil. In the same study, the median survival for gemcitabine treated patients was 5.65 months versus 4.41 months for 5FU treated subjects. Comparative 12-month survival was also increased in gemcitabine patients (18% to 2% for 5FU) (Burris, et al., 1997). Gemcitabine is used either alone or in combination with other agents in the treatment of pancreatic cancer.



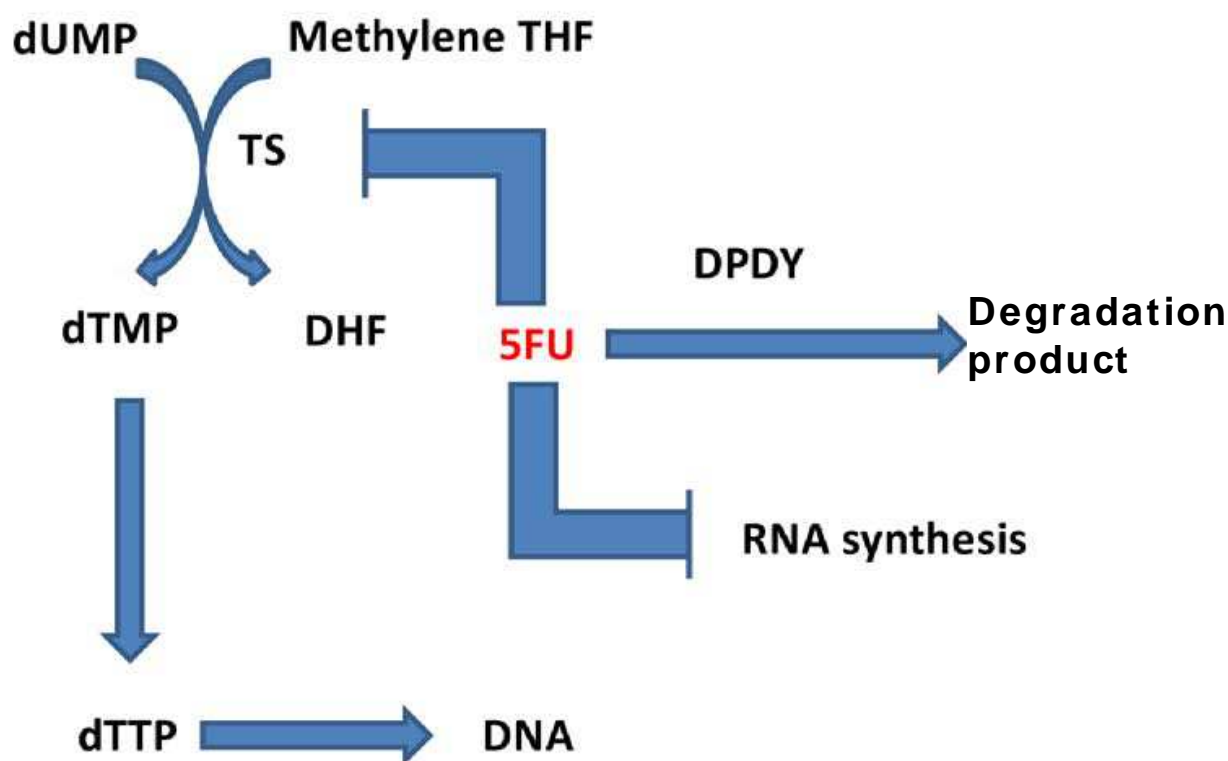
dCK: deoxycytidine kinase; dFdCMP: difluorodeoxycytidine monophosphate; dFdCDP: difluorodeoxycytidine diphosphate; dFdCTP: difluorodeoxycytidine triphosphate; CTP: cytidine triphosphate; CDP: cytidine diphosphate.

Fig. 1. Gemcitabine mechanism of action

Gemcitabine mainly acts by three mechanisms as shown in figure 1. First, it forms dFdCTP (di-fluorodeoxycytidine triphosphate) by the action of enzyme deoxycytidine kinase (dCK). dFdCTP competes with cytidine triphosphate (CTP) to get incorporated into the DNA. Secondly, its diphosphate metabolite (dFdCDP) inhibits ribonucleotide reductase, further preventing the formation of triphosphate nucleotide. Thirdly, triphosphate metabolite (dFdCTP) inhibits DNA polymerase which is important for DNA repair (Huang, *et al.*, 1991; Kang and Saif, 2008). Gemcitabine enters the cell via human equilibrative nucleotide transporter 1 (hENT1) (Mackey, *et al.*, 1998). Patients with detectable expression of hENT had significantly longer survival than patients with low levels or absence of this protein (Spratlin, *et al.*, 2004).

2.2 5-Fluorouracil (5FU)

5FU belongs to the antimetabolite class of chemotherapeutic drug and is structurally similar to the uracil molecule with an additional fluorine atom at position 5. The drug 5FU gets mis-incorporated into DNA and RNA and also prevents nucleic acid synthesis by inhibiting the enzyme thymidylate synthase (TS). 5FU was the first drug to be approved as an adjuvant therapy for the treatment of pancreatic cancer. Combination of 5FU to radiation therapy increased the survival (10 months vs 6 months, no drug treatment) of pancreatic cancer patients with locally unresectable cancer (Kalser and Ellenberg, 1985; Moertel, *et al.*, 1981).



dUMP: deoxyuridine monophosphate; THF: tetrahydrofolate; dTMP: deoxythymidine monophosphate; DHF: dihydrofolic acid; DPDY: dihydropyrimidine dehydrogenase; dTTP: deoxythymidine triphosphate; TS: thymidylate synthetase; 5FU: 5-fluorouracil.

Fig. 2. 5FU mechanism of action

Due to structural similarity, 5FU enters the cell using the same facilitator transporter as uracil (Diasio and Harris, 1989; Santi, et al., 1974; Wohlhueter, et al., 1980). Once inside the cell (Fig. 2), it forms various metabolites. Among these metabolites, fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP) and fluorouridine triphosphate (FUTP) are the active metabolites which disrupt RNA synthesis and inhibit TS. 5, 10-Methylenetetrahydrofolate (CH₂THF) acts as the methyl donor for the conversion of dUMP to dTMP. 5FU binds to TS resulting in depletion of deoxythymidine triphosphate (dTTP) which further causes depletion in the levels of dATP, dCTP and dGTP. Imbalance in the ATP/dTTP ratio leads to disruption of DNA synthesis and repair (Diasio and Harris, 1989; Howell, et al., 1981; JL, 1996; Santi, et al., 1974).

3. Anticancer drug specific resistance

3.1 Gemcitabine resistance

Resistance to chemotherapeutic agents is observed commonly in mammalian tumors. Resistance can arise *de novo* or can be acquired after drug exposure. The vast genetic heterogeneity of cancer cells is considered to be the reason for the acquired resistance (Casa, et al., 2008). Cancer cells can acquire resistance against a drug through various mechanisms. It can prevent a drug’s entry into the cell or increase its exit from the cell. Once the drug is inside the cell, it can be degraded into inactive metabolites by over-expression of the catabolic enzyme or by inhibiting the activity of the enzyme responsible for converting the pro-drug into an active agent (Gottesman, 2002). Drug resistance is one of the important factors responsible for low survival rate of pancreatic cancer patients. Numerous studies over the past two decades have suggested that pancreatic cancer is associated with various genetic alterations which contribute to its resistant characteristics (Almoguera, et al., 1988; Feldmann, et al., 2007; Hruban and Fukushima, 2007). Some of these mechanisms are listed in table 1:

Mechanisms	5-Fluoruracil (Santi, McHenry et al. 1974; Wohlhueter, McIvor et al. 1980; Howell, Mansfield et al. 1981; Diasio and Harris 1989; Lowe, Ruley et al. 1993; JL 1996; Ahnen, Feigl et al. 1998; Lenz, Hayashi et al. 1998; Bunz, Hwang et al. 1999; Eisold, Linnebacher et al. 2004; Zhang, Yin et al. 2008)	Gemcitabine (Bergman, Pinedo et al. 2002; Galmarini, Clarke et al. 2002; Garcia-Manteiga, Molina-Arcas et al. 2003; Yokoi and Fidler 2004; Nakano, Tanno et al. 2007)
MOA related	Thymidylate synthetase	Ribonucleotide reductase
Transporters	MRP 3 and 5	MDR1
Molecular	Akt, src	Akt, NF κB, src

Table 1. Suggested mechanisms for drug resistance in pancreatic cancer

Some of the markers of gemcitabine resistance include decreased expression of dCK, increased levels of competing dCTP, low levels of hENT, and alteration of PI3K/Akt/NFκB pathway, FAK, and hypoxia (Almoguera, et al., 1988; Feldmann, et al., 2007; Hruban and Fukushima, 2007)

3.2 5FU resistance

Resistance to 5FU induced cytotoxicity or cancer cells' response to 5FU treatment is controlled/characterized by various factors (Kang and Saif, 2008; Zhang, et al., 2008), as discussed below.

3.2.1 Thymidylate Synthase (TS)

TS controls several aspects of a tumor's response to 5FU therapy. Increase in the TS level can reduce the accumulation of activated metabolites of 5FU and hence reduce toxicity. Also, mutation of the enzyme can decrease 5FU's affinity to TS. TS overexpression is considered as a major mechanism responsible for 5FU resistance. Decreased levels of reduced folate substrate, 5,10-methyltetrahydrofolate, also reduces 5FU response.

3.2.2 Dihydropyrimidine dehydrogenase (DPDY)

Increase in the activity of DPDY can increase the catabolism of 5FU leading to its inactivation. Other studies have shown that low-DPDY tumors are more responsive to 5FU treatment.

3.2.3 Slow down of cell cycle

This mechanism can prevent the incorporation of 5FU metabolites in the cells and provide the cells with sufficient time to correct the misincorporated nucleotides.

3.2.4 Human Equilibrative Nucleoside Transporters (hENT)

These transporters are important for delivery of 5FU from the extra-cellular space into cells. Levels of hENT1 has been correlated with pancreatic cancer cell sensitivity to 5FU response and few studies have suggested that hENT plays an important role in 5FU resistance. hENT1 mRNA levels are suggested to be a useful marker to predict 5FU sensitivity (Kang and Saif, 2008; Zhang, et al., 2008)

3.2.5 Other factors causing 5FU resistance

Mutated p53

This tumor suppressor gene, which is mutated in 30-70 % of pancreatic cancer cases, can affect 5FU response in pancreatic cancer cases. Wild type p53 expression is required for 5FU-induced apoptosis and p53 status of tumor cells can determine the response to 5FU-based chemotherapy (Ahnen, et al., 1998; Bunz, et al., 1999; Lenz, et al., 1998; Lowe, et al., 1993). Another study found that transfection of pancreatic cancer cells with wild type p53 synergistically enhances the cytotoxicity of 5FU both *in vivo* and *in vitro*. The same study also showed that pancreatic cancer cell line with wild type p53 status was more sensitive to 5FU as compared to the p53 mutated line (Eisold, et al., 2004).

Mutated EGFR-Ras-MAPK cascade

This signaling pathway is important for growth, survival and proliferation of cells. The signaling cascade is found to be mutated at various levels in pancreatic cancer, leading to

over-activation of the pathway and hence increased growth and proliferation of the cancer cells (References). Protein expression of members of this pathway can modulate the cytotoxic effect of 5FU on pancreatic cancer cells. Blockade of EGFR increases the cytotoxicity of 5FU in both *in vivo* and *in vitro* conditions (Overholser, *et al.*, 2000). Furthermore, activation of MAPK reduces the sensitivity of pancreatic cancer cells to 5FU treatment *in vitro* (Wey, *et al.*, 2005). K-ras mutation is the hallmark of pancreatic cancer and occurs early during the development of pancreatic neoplasia. Ras-mutated pancreatic cells have shown to respond better to 5FU treatment as compared to their non-ras-transformed counterparts (Hiwasa, *et al.*, 1996).

4. Relationship of resistance to cellular processes

The mechanisms involved in drug resistance in pancreatic cancer are different for different drugs. In a broad sense, drug resistance in pancreatic cancer can be linked to modulation of enzymes, receptors, DNA repair and other processes. These are discussed in depth in this section. For drugs to be effective, they should be transported successfully into the cells, reach their respective effective concentrations and should form their active forms before they are transported out of cells (Longley, *et al.*, 2003; Plunkett, *et al.*, 1995)

4.1 Enzyme linked mechanisms

The expression levels of the enzyme DCK determines the patient survival and the sensitivity of a tumor to gemcitabine (Hagmann, *et al.*, 2010a; Plunkett, *et al.*, 1995). HuR is a RNA-binding protein that modulates the translation of DCK mRNA and multiple other proto-oncogenic proteins in cancer cells (Williams, *et al.*, 2010). Modulation of mRNA is dependent on stress conditions and includes the presence of therapeutic agents. Expression of HuR increases in pancreatic cancer cells treated with gemcitabine and an increased level of HuR in the cytoplasm is a marker of gemcitabine sensitivity (Costantino, *et al.*, 2009). pp32 is a protein phosphatase and tumor suppressor gene that regulates the post-transcriptional activity of mRNA to which the HuR protein binds. Although the exact mechanism by which pp32 regulates HuR is yet to be unveiled, researchers have cited possible ways by which pp32 regulates the post-transcriptional changes of transcribed mRNA. The possibilities include: a) disrupting the interaction of HuR with mRNA in the nucleus, b) inhibiting translocation of the HuR-bound mRNA into cytosol and thereby inhibiting translation of oncogenic proteins, and other possible mechanisms (References). Overexpression of pp32 can result in inhibition of dCK mRNA translation and hence poor gemcitabine efficacy (Williams, *et al.*, 2010).

Thymidylate synthetase (TS) controls a tumor's response to 5FU therapy. Increase in the TS level can reduce the accumulation of activated metabolites of 5FU and hence reduce toxicity. Additionally, mutation of the enzyme can decrease its affinity to TS. TS overexpression is considered as a major mechanism responsible for 5FU resistance. Decreased levels of reduced folate substrate, 5,10-methyltetrahydrofolate, also reduces 5FU response (Zhang, *et al.*, 2008).

Increase in the activity of dihydropyrimidine dehydrogenase (DPDY) can increase the catabolism of 5FU leading to its inactivation. Few studies have shown that low-DPDY tumors are more responsive to 5FU treatment.

5FU resistance can result from induction of TS levels upon administration of 5FU which brings about the activation of autoregulatory feedback pathway where the TS protein regulates the translation of its mRNA. The salvage pathway involving the enzyme thymidine kinase, the biochemical reaction in which thymidylate is derived from thymidine could be one of the ways the cells acquire resistance to 5FU. (Zhang, *et al.*, 2008)

4.2 Receptor linked mechanisms

4.2.1 Drug uptake

Due to structural similarity to the nucleosides, a drug can enter the cells through uptake by the concentrative nucleoside transporters (CNT's) and equilibrative nucleoside transporters (ENT's). CNT1 and CNT3 have high affinity for gemcitabine whereas ENT1 and ENT2 have lower affinity for gemcitabine. Pancreatic tumor cells exhibit higher expression levels of ENT1 but low to negligible levels of CNT 3. This phenotype affects the transport of gemcitabine into the cancer cells and ultimately gemcitabine's action on DNA and RNA synthesis. The expression levels of ENT1 and CNT3 provide an index of patient survival after gemcitabine treatment (Hagmann, *et al.*, 2010b).

In the case of 5FU, resistance was found to be imparted due to overexpression of ENT1. A study using 7 pancreatic cancer cell lines (AsPC1, BxPC3, MiaPaCa-2, PSN1, Panc1, PCI6, and KMP-4) reported an increased expression of ENT1 mRNA, which correlated with the IC₅₀ of 5FU in the AsPC1 cell line, a cell line most resistant to 5FU among the cell lines tested (Tsujiie, *et al.*; 2007). Thymidylate synthase (a target of 5FU) and dihydropyrimidine dehydrogenase (DPDY), which metabolizes 5FU, were not overexpressed with simultaneous overexpression of ENT1: this phenotype implies that the toxicity of 5FU was countered by increased uptake of nucleosides and nucleotide bases through the salvage pathway (Tsujiie, *et al.*, 2007). It is therefore widely accepted that ENT1 overexpression serves as a marker of 5FU resistance (Huber-Ruano and Pastor-Anglada, 2009; Tsujiie, *et al.*, 2007).

4.2.2 Drug efflux

Drug efflux is one of the potential means by which cancer cells exhibit chemoresistance: it is mediated by a family of proteins, ATP binding cassette (ABC) proteins, which involve ATP utilization (Wu, *et al.*, 2008). The human genome encodes 49 members of this protein family and about 15 proteins are implicated in cancer chemoresistance. These transporters have an intracellular nucleotide binding domain that hydrolyses ATP and results in conformational change in its structure leading to the transmembrane domain forming a channel-like structure through which the drug is effluxed to the extracellular space (Santisteban, 2010). P glycoprotein, multidrug resistance associated protein (MRP1) and breast cancer resistance protein (BCRP) constitute the universal drug efflux transporters (Santisteban, 2010; Wu, *et al.*, 2008).

The efflux of gemcitabine and its triphosphate metabolite is mediated by multidrug resistant protein 5 (MRP5), which is a member of the ATP binding cassette (ABC) family of proteins. Evidences in support of the role of MRP3, MRP4 and MRP5 in the efflux of etoposide, 5FU and gemcitabine suggest that these MRP's are directly linked with the resistance phenotype (Hagmann, *et al.*, 2010a; Hagmann, *et al.*, 2010b). Transcriptional regulation of MRP's by nuclear factor like 2 protein (Nrf2) is an important target to overcome resistance because

overexpression of Nrf2 is associated with increased resistance of cells towards chemotherapy-induced cell death (Hagmann, *et al.*, 2010a).

Evidences in support of overexpression of these transporters in cancer stem cells and failure of the classical concept of direct inhibition of transporters in resistant cells using the first generation inhibitors like verapamil and quinidine and second generation inhibitors like valspodar and biricodar have led researchers to focus on the pathways that may be involved (Santisteban, 2010).

4.3 Role of hedgehog pathway in resistance

Hedgehog signaling between the tumor cells and stromal cells brings about a desmoplastic reaction where the stromal fibroblasts secrete collagen in higher amounts and result in fibrosis of the surrounding stromal tissue. Hedgehog signaling also has a key role in promoting epithelial mesenchymal transition and the acquisition of mesenchymal phenotype is associated with over expression of ABC transporters in breast cancer and in pancreatic adenocarcinoma (Santisteban, 2010). Studies using KPC (Kras and p53 mutant) mice with PDAC (Pancreatic Ductal Adenocarcinoma) highlighted the role of hedgehog pathway in resistance aided by the desmoplastic reaction where the mean vascular density to the tumor tissue decreased and resulted in decreased delivery of gemcitabine to the tumor tissue (Olive, *et al.*, 2009). Use of a pathway inhibitors like cyclopamine derivatives, that inhibit the protein smoothened, which is downstream of hedgehog signaling prevents transcriptional activation of target genes that bring about resistance by promoting overexpression of ABC transporters and by preventing desmoplasia (Olive, *et al.*, 2009; Santisteban, 2010).

4.4 Role of MAPK in resistance

Three types of mitogen activated protein kinases (MAPK) have been identified in humans, including the extracellular signal regulated kinases (ERK), c-Jun N-terminal kinases and the p38 MAP kinases and all these act by serine/threonine phosphorylation of target proteins (Wagner and Nebreda, 2009). Interestingly, ERK pathway activation promotes survival while activation of JNK and p38 MAPK pathways induce apoptotic cell death as they are activated under stress conditions (Wagner and Nebreda, 2009; Zhao, *et al.*, 2006a). Involvement of MAPKinase pathways in acquired chemoresistance has been studied by researchers but a clear idea of the mechanisms involved has yet to be established. ERK pathway which is downstream of EGFR signaling, promotes cell survival through its pro-survival signals which may be responsible for chemoresistance. Employing the SW 1990 cell line, Zhao *et al* demonstrated that ERK signaling regulates chemoresistance depending on the chemotherapeutic agent. Resistant cell lines exhibit a higher level of ERK activity as compared to sensitive cell lines and that inhibition of ERK pathway resulted in 5FU sensitivity but increased GEM resistance. 5FU acts by activating intrinsic apoptotic pathway whereas GEM induces cell death by activating extrinsic apoptotic pathway (Zhao, *et al.*, 2006a).

4.5 Role of PI3K/Akt pathway in resistance

As opposed to earlier notions that drug resistance arises by increased drug metabolism or efflux or decreased transport of the drugs into the cells, Ng *et al.*(2000), using PK1 and PK8 cell lines, demonstrated that the anti-apoptotic advantage of cells towards gemcitabine is

conferred not by the classical resistance mechanisms alone but also by the activation of PI3K/Akt pathway when the intracellular concentration of gemcitabine was found to be effective to affect DNA and cell cycle (Ng, *et al.*, 2000). PI3K/Akt pathway activation stems from phosphorylation of receptor tyrosine kinases and the regulatory subunit of PI3K, the p85 interacts with the active tyrosine kinase domains for activation. Activation of PI3K results in phosphorylation of its substrates which includes phosphoinositides and protein kinase B (PKB), otherwise called Akt. Phosphorylation of Akt and its subsequent nuclear translocation results in transcriptional activation of genes that promote cell survival (Hennessy, *et al.*, 2005; Ng, *et al.*, 2000). Apart from this mechanism, the phosphorylated Akt is also shown to inactivate the pro-apoptotic protein BAD by phosphorylating it and thereby giving the anti-apoptotic advantage to the cells. In addition, the activation of PI3K can also occur by interaction of the catalytic subunit of PI3K (p110 subunit) with constitutively active membrane bound Ras (Ng, *et al.*, 2000).

4.6 Role of Zeb-1 in resistance

Zeb1 is a transcriptional suppressor of E-cadherin which is involved in cell-cell adhesion and is the marker of epithelial cells. By doing so, it promotes epithelial-mesenchymal transition (EMT) upon which the cells metastasize and form secondary tumors (Wellner, *et al.*, 2010). Epithelial mesenchymal transition is a process by which the tumor cells with epithelial lineage origin acquire the mesenchymal phenotype. This process gives them an advantage of migrating from the primary tumor site into the blood stream and develop secondary tumors at various sites depending on the availability of suitable microenvironment. The whole process is called metastasis which is dependent on EMT. During EMT, the epithelial cells lose epithelial cell surface markers, express mesenchymal markers and undergo cytoskeletal remodeling in which the cell polarity, a characteristic of the epithelial cells, is lost and the cells acquire an invasive phenotype. Downregulation of E-cadherin and upregulation of mesenchymal markers vimentin, smooth muscle actin, gamma-actin, beta-filamin, talina and extracellular matrix components like fibronectin and collagen precursors are key features of EMT (Christiansen and Rajasekaran, 2006; Kalluri and Weinberg, 2009).

Recent studies on the role of Zeb-1 by Arumugam *et al.* (2009) confirmed the role of Zeb-1 not only in promoting metastasis but also in drug resistance. This group found that the cancer cell lines which are sensitive to gemcitabine (L3.6pl, BxPC3, CFPAC, SU86.86) are more sensitive to 5FU and cisplatin as compared to the gemcitabine-resistant cancer cell lines (PANC-1, Hs766T, AsPC-1, MIAPaCa-2, MPanc96). When Zeb-1 activity was silenced using siRNA in PANC1, MIAPaCA-2 and Hs766T cell lines, there was increased apoptosis in these cell lines on treatment with gemcitabine, 5FU or cisplatin, separately. This finding suggests an important role for Zeb-1 in drug resistance. Erlotinib is an EGFR inhibitor that is used in combination with gemcitabine to treat pancreatic cancer. Resistance to EGFR inhibition is a hallmark of EMT which can be reverted by silencing the activity of Zeb-1, which in turn increases sensitivity of the cells to EGFR inhibition (Arumugam, *et al.*, 2009).

4.7 Role of NFκB in inducing gemcitabine resistance

Nuclear factor kappa light chain enhancer of activated B-cells (NFκB) is a complex involved in important cellular processes like inflammation, apoptosis regulation and stress

adaptation. In the cell, it is present tightly bound to inhibitory proteins like I κ B α and is released in response to stimuli that bring about activation of I κ B kinase (IKK). The free cytosolic NF κ B then translocates into the nucleus where it regulates gene expression. The role of NF κ B in gemcitabine resistance has been demonstrated. Arlt *et al.* (2003), using gemcitabine resistant (BxPC3 and Capan1) and gemcitabine sensitive (T3M4 and PT45-P1) cell lines, found that the autocrine loops for generation of NF κ B play an important role in gemcitabine resistance. Employing NF κ B inhibitors (MG132 or sulfasalazine), they found basal NF κ B levels confer resistance and the basal NF κ B levels are not affected by the activated or inactive state of PI3K/ Akt pathway (Arlt, *et al.*, 2003).

4.8 Role of notch signaling in chemoresistance

Notch signaling is a developmental pathway which is implicated in organogenesis, development of nervous and vascular systems and hematopoietic stem cell generation in adults (Chiba, 2007). Notch signaling is important for self-renewal of stem cell and along with Wnt signaling, it prevents terminal differentiation of cells (Kato, 2007). Overactivity of Notch signaling is observed in various hematopoietic and solid tumors leading to proliferation, and inhibition of differentiation and apoptosis. In pancreatic cancer cells, Notch signaling is implicated in drug resistance. Wang *et al.* found that components of Notch signaling pathway are upregulated in gemcitabine resistant pancreatic cancer cells and are associated with increase invasiveness (Bao, *et al.*, 2011b; Wang, *et al.*, 2009). Yao and Qian (2010) observed that inhibition of Notch3 by the siRNA approach increases gemcitabine-induced cytotoxicity in pancreatic cancer cell via affecting the PI3K/ Akt pathway. The studies mentioned above strongly suggest that cancer stem cell signaling pathways could be attractive targets for increasing their sensitivity to chemotherapeutic agents (Bao, *et al.*, 2011b).

4.9 Miscellaneous other mechanisms

A role of for the glycoprotein, mucin MUC4, in pancreatic cancer cell resistance to the first line chemotherapeutic agent, gemcitabine has recently emerged. Mucin MUC4 is overexpressed on the membrane of pancreatic cancer cells but not normal pancreatic cells (Santisteban, 2010). Studies on this glycoprotein's involvement in gemcitabine resistance have revealed the interaction of this glycoprotein with the HER2 receptor and the subsequent activation of ERK pathway and phosphorylation of the pro-apoptotic protein BAD which inhibits apoptosis induced by gemcitabine (Ponnusamy, *et al.*, 2008; Santisteban, 2010).

5. Overall strategies to overcome resistance

5.1 miRNA

miRNA (miR) are 18-24 nucleotide-long RNA molecules which can regulate the translation of mature RNA into protein. They are synthesized as a 60-80 nucleotide-long, hairpin-shaped RNA molecule which is transported to the cytoplasm where it undergoes processing to form 18-24 nucleotide-long double stranded RNA molecule. One of the strands then interacts with RNA-induced silenced complex (RISC) and targets RNA translation. Various miRNAs have been demonstrated to play a role in development and cancer progression. Dysregulation of miRNAs has also been observed in pancreatic cancer tissues and cell lines. Bloomston *et al.* (2007) found that the levels of miRNAs can be used to differentiate between

pancreatic tumor, chronic pancreatitis and benign pancreatic tissue. They also found that the expression of six miRNAs can predict the survival of the pancreatic cancer patients (Bloomston, et al., 2007). Zhang et al. (2009) profiled the levels of 95 miRNAs in pancreatic tumors, pancreatic cancer cell lines, pancreatic tissues and pancreatic ductal epithelial cells. They found that the expression of 8 miRNAs were significantly upregulated in pancreatic cancer tissues and cancer cell lines compared to the pancreatic tissues and pancreatic ductal cells (Zhang, et al., 2009).

Deregulated miRNA levels could serve as attractive targets for treatment of pancreatic cancer. Moriyama et al. (2009) found that the level of miR21 is upregulated in pancreatic cancer cells and its inhibition decreases proliferation, invasion, chemoresistance and induces cell cycle arrest and apoptosis in pancreatic cancer cells. On the other hand, Banerjee et al., (2007) found that the expression of miRNAs can be modulated by natural compounds which reduce EMT and chemoresistance in pancreatic cancer cells. These studies strongly suggest that deregulated levels of miRNA in pancreatic cancer can be exploited as putative therapeutic targets for overcoming pancreatic cancer drug resistance.

5.2 Stem cell signaling

Some studies have suggested that a tumor comprises of heterogeneous populations of cells rather than just homogenous cell types. One subset is suggested to be distinct cells that have limited proliferative capacity but are responsible for initiation, progression and differentiation of cancer cells. Due to their ability to self-renew and differentiate like stem cells, these cells are termed as “cancer stem cells.” There have been attempts with some successes to isolate the cancer stem cells so that they can be employed to elucidate genotypic and phenotypic characteristics as well as develop effective therapies to target to them because of their ability to self-renew and their resistance to conventional chemo- and/or radiation therapies.

Li et al. (2007) isolated pancreatic cancer cells which were highly tumorigenic and had the ability to self-renew based on their cell surface markers. These cells (CD44⁺CD24⁺ESA⁺) comprises of 0.2-0.8% of all pancreatic cancer cells and were able to produce differentiated progeny. Similarly, Herman et al. (2007) isolated pancreatic cancer stem cells which were CD133⁺.

The cancer stem cells are known to be resistant to conventional chemo-radiation therapies. Michor et al. showed that a subpopulation of chronic myeloid leukemia stem cells were resistant to imatinib (Michor, et al., 2005). In glioblastoma, enrichment of CD133⁺ cells was observed after treatment with ionizing radiation. These cells activate DNA damage response upon irradiation and therefore are resistant to ionizing radiation (Bao, et al., 2006). Similarly, enrichment of cells with stem cell characteristics is observed on treatment of pancreatic cancer with radio- or chemotherapy (Hermann, et al., 2007; Li, et al., 2007).

5.3 Natural compounds for reversing resistance

Dietary habit of individuals has been correlated with development of pancreatic cancer. High cholesterol diet increases the risk of pancreatic cancer (Baghurst, et al., 1991; Ghadirian, et al., 1991; Howe, et al., 1992; Stolzenberg-Solomon, et al., 2002). Diet rich in fruits and vegetables is associated with reduced risk while intake of red meat is associated with

increased risk of developing pancreatic cancer (Boyle, *et al.*, 1989; Inoue, *et al.*, 2003; Ohba, *et al.*, 1996; Tavani, *et al.*, 2000).

Various natural compounds have been tested for their anti-pancreatic cancer properties in laboratory settings. Kunnumakkara *et al.* (2001) showed that curcumin inhibits NF κ B activation and increases the cytotoxicity of gemcitabine *in vitro* and *in vivo*. That study also found that curcumin decreases the microvascular density thereby decreasing angiogenesis (Kunnumakkara, *et al.*, 2007). NF κ B is involved in mediating resistance against gemcitabine and TRAIL, which may explain the increase in cytotoxicity. Curcumin also increased the accumulation of MRP5 substrate intracellularly in MRP5 positive cells; however, in the absence of MRP5, drug accumulation was not observed. Additionally, curcumin increased the cell's sensitivity to 5FU (Li, *et al.*, 2010). Furthermore, hydroethanolic extract of curcumin (Tumeric Force) was more effective than curcumin in this effect.

Another group of natural compounds which are currently being investigated are isoflavones. One of the most well studied isoflavones, genistein has been tested extensively in pancreatic cancer. Various groups have shown that treatment with genistein controls proliferation, mitogenic signaling, invasion, migration and induces apoptosis in pancreatic cancer. Benerjee *et al.* (2007) showed that genistein augments *in vitro* and *in vivo* efficacy of cisplatin in pancreatic cancer (Banerjee, *et al.*, 2007). Previously, genistein was known to affect the activation of NF κ B via the Akt pathway (El-Rayes, *et al.*, 2006), which have been shown to be involved in pancreatic cancer drug resistance. Natural compounds (e.g., genistein, curcumin) have also been shown to inhibit the hedgehog and Notch signaling which provide the cancer cells with stem-cell like property of self-renewal and resistance (Slusarz, *et al.*, 2010). A recent study noted upregulation of FOXM1, increased EMT, and cancer stem cell phenotype in pancreatic cancer (Bao, *et al.*, 2011a). Treatment with natural compounds also reduced the levels of FOXM1 in pancreatic cancers.

Apart from the above mentioned approaches and based on the literature cited in this chapter, there are some other strategies to overcome resistance including potential targets and areas for drug discovery like developing agents that regulate Nrf2 activity selectively in tumor cells, agents that inhibit interaction between mucin MUC4 and HER2, selective inhibition of hedge hog pathway in the tumor cells, selective inhibition of PI3K/Akt pathway in tumor cells, combination of anti-NF κ B agents with gemcitabine and Zeb1 silencing. Targeting sphingolipid metabolism is another approach to overcome resistance to gemcitabine (Guillermet-Guibert, *et al.*, 2009). Recent renewed interests in the metabolic phenotypes of pancreatic and other cancers have raised possibilities of metabolic pathway(s) as drug targets for new anti-cancer drug discovery.

6. Conclusions

Although these strategies to overcome resistance to drugs are crucial for improving the outcome of chemotherapy, there is an urgent need to achieve early detection of pancreatic cancer. Finding novel biomarkers for detecting pancreatic cancer should be emphasized. Recent renewed interests in the metabolic phenotypes of pancreatic and other cancers have raised possibilities of metabolic pathway(s) as targets for strategies for developing agents for early tumor detection to addition to exploiting them as targets for new anti-cancer drug discovery.

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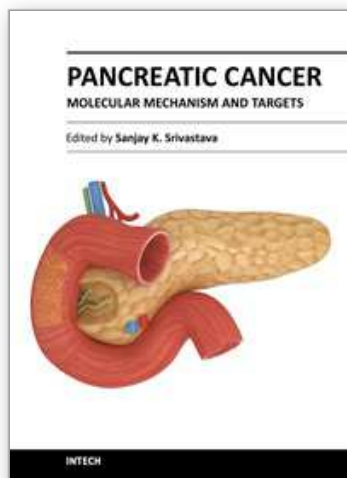
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This book provides the reader with an overall understanding of the biology of pancreatic cancer, hereditary, complex signaling pathways and alternative therapies. The book explains nutrigenomics and epigenetics mechanisms such as DNA methylation, which may explain the etiology or progression of pancreatic cancer. Book also summarizes the molecular control of oncogenic pathways such as K-Ras and KLF4. Since pancreatic cancer metastasizes to vital organs resulting in poor prognosis, special emphasis is given to the mechanism of tumor cell invasion and metastasis. Role of nitric oxide and Syk kinase in tumor metastasis is discussed in detail. Prevention strategies for pancreatic cancer are also described. The molecular mechanisms of the anti-cancer effects of curcumin, benzyl isothiocyanate and vitamin D are discussed in detail. Furthermore, this book covers the basic mechanisms of resistance of pancreatic cancer to chemotherapy drugs such as gemcitabine and 5-flourouracil.

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