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Investigational agents to enhance the efficacy of chemotherapy or radiation in pancreatic cancer

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ABSTRACT

Pancreatic cancer (PC) continues to be a fatal malignancy. With standard treatments having modest impact, alternative courses of actions are being investigated such as enhancing the efficacy of standard treatment through sensitization of PC cells to chemotherapy or radiation. This review emphasizes investigational agents that increase the responses to chemotherapy or radiation in PC models. Our group has extensively investigated on Curcumin (Cur), analogs (EF31, UBS109, and L49H37), nanoparticles and a small molecule Tolfenamic acid (TA) for enhancing therapeutic efficacy in both *in vitro* and *in vivo* assays. Cur has a low level of toxicity and promising anti-cancer activity, however, its clinical development has been limited by low bioavailability. Cur analogs and nanoparticles were synthesized to improve Cur's efficacy and bioavailability. These compounds were found to be effective in enhancing the therapeutic effects of chemotherapy in pre-clinical models. Small molecules such as NSAIDs have also been tested for the anti-cancer activity and induction of response of chemotherapy and radiation. Interest in TA, a NSAID, has recently increased due to promising preclinical data demonstrating its anti-cancer properties with minimum toxicity. TA also synergistically increased the response of XRT in PC cells and in an orthotropic mouse model. With strong preclinical evidence, research aimed at developing less toxic therapies for PC using Cur analogues or TA is ready for translation into clinical testing.

1. Introduction

Cancer research continues to advance the outcome of patients with cancer as reflected by the higher survival rates and better quality of life. In an effort to enhance outcomes, researchers are focused on evaluating therapies with more effectiveness as well as lesser toxicities. Despite recent discoveries and advances in medicine, pancreatic cancer (PC) has a very poor prognosis that urgently requires novel therapeutic approaches. Currently, the five-year survival rate for PC is 8% (Siegel et al., 2017). This dismal statistic is attributed to several factors; including when a patient is diagnosed. PC tends to metastasize early in the course of disease leading to typically being diagnosed at late stages. Surgical resection is not even a feasible route for most patients with PC (Hidalgo et al., 2015).Current standard treatment options include either chemotherapy or a combination of chemotherapy and radiation (XRT), which offer a modest benefit. A commonly used chemotherapeutic is the nucleoside analog gemcitabine. Gemcitabine works by inhibiting DNA synthesis, thereby, slowing cancer growth and progression. Unfortunately, gemcitabine has only limited benefits before patients begin to develop resistance within a relatively short time (Binenbaum et al., 2015; Wang et al., 2014). Therefore, there is an urgent demand for therapies that are more effective. An effective approach could be to use low toxic agents in combination with standard cancer therapies in order to sensitize the cells. This would make the overall treatment more efficient and less toxic for the patient.

2. Investigational agents tested along with chemotherapy and/or radiation

As presented in Table 1, several agents such as 3, 3′-Diindolylmethane (Banerjee et al., 2009b; Kim, 2016), Folinic acid (Oettle et al., 2014), Low molecular weight heparin (Icli et al., 2007), and Thymoquinone (Banerjee et al., 2009a) were tested to enhance the cytotoxicity of chemotherapy in PC cells. Cerium oxide (Wason et al., 2013), Metformin (Wang et al., 2015) and Tolfenamic acid (Konduri et al., 2009) were used for sensitizing PC cells to XRT, and Chk1

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Table 1
Selected list of investigational agents that are tested for improving the efficacy of chemotherapy or radiation therapy or both.

S.No	Agent	Improves the Effect of Chemo/Radiation	Reference(s)
1.	3, 3′-Diindolylmethane	Cisplatin, Gemcitabine, Oxaliplatin	Apte and Wilson (2012); Banerjee et al. (2009a)
2.	Folinic acid	Oxaliplatin, 5FU	Banerjee et al. (2009b)
3.	Low molecular weight heparin (LMWH)	Cisplatinum and gemcitabinecombination	Bao et al. (2012)
4.	Thymoquinone	Gemcitabine, Oxaliplatin	Bao et al. (2011)
5.	Curcumin	Gemcitabine	Kausar et al. (2015)
6.	Cerium oxide	Radiation	Binenbaum et al. (2015)
7.	Metformin	Radiation	Chambard et al. (2007)
8.	Tolfenamic acid	Radiation	Deguchi, (2015)
9.	Chk1 Inhibitor MK8776	Chemotherapy & Radiation	Devassy et al. (2015)
10.	Nimotuzumab	Chemotherapy & Radiation	Engelke et al. (2013)
11.	WEE1 inhibitor AZD1775	Chemotherapy & Radiation	Friedman et al. (2009)

Inhibitor MK8776 (Engelke et al., 2013), Nimotuzumab(Gao et al., 2016) and WEE1 inhibitor AZD1775 (Kausar et al., 2015) for both chemo and irradiation. Studies from our group demonstrated that the natural plant product Curcumin (Cur), Cur analogs (EF31, UBS109, and L49H37), and small molecule Tolfenamic acid (TA) have all been found to exhibit anti-cancer properties and low toxicity in preclinical studies for PC, thus, making them attractive anti-cancer agents for PC, This review article provides an update on research conducted with Cur, Cur analogs and TA for their anti-cancer activity in PC and also their ability to induce the response of chemo-radiation therapy.

3. Curcumin and its anti-cancer properties

The natural phenol, Cur, is a plant (turmeric), *Curcuma longa* extract. It is widely used as cooking spice in the Asian sub-continent. Cur is known for its anti-oxidant properties and pharmacological safety and has been tested as an anti-cancer agent (Aggarwal et al., 2003; Deguchi, 2015; Devassy et al., 2015; Hossain et al., 2012). Among the mechanisms proposed for Cur's anticancer activity, the most predominant one is the disruption of nuclear factor (NF)-κB activity. Li et al. (2004) first demonstrated that Cur inhibits growth of cancer cells following time/dose-dependent manner and has a pro-apoptotic effect against PC cells (Li et al., 2004). Cur treatment had increased apoptosis and the expression of cleaved poly (ADP-ribose) polymerase (PARP). The reduction in of cell growth and upregulation of apoptosis observed due to Cur treatment may be partially due to the inhibition of NF-κB, a TF that helps facilitate transcription for growth-regulatory genes. Constitutively active NF-κB has been found to contribute to tumorigenesis in PC and thus, serves as a potential target (Prabhu et al., 2014). Therefore, Li et al. (2004) also investigated Cur's effect on NF-κB. Among the several genes it regulates is cyclooxygenase (COX)-2, an enzyme involved with arachidonic acid metabolism. COX-2 is responsible for the formation of Prostaglandin E2 (PGE-2). COX-2 is overexpressed in PC which impacts proliferation and metastasis (Yip-Schneider et al., 2000). Thus COX-2 was another protein of interest in this malignancy. Experiments with five cell lines that had constitutively active NF-κB demonstrated that when compared to untreated cells, Cur treated cells showed a decrease in NF-κB binding and affecting its activity. Cur also alternated protein expression of NF-κB's downstream targets. Cur treatment decreased COX-2 and PGE-2 expression levels. In other studies, Cur treatment was shown to increase phosphorylation of H2AX accompanied by activation of ATM/Chk1 that results in G2/M arrest and apoptosis (Sahu et al., 2009). Cur also inhibits STAT3 activation and downregulates BIRC5 expression (Glienke et al., 2010). NF-κB activity is influenced by the Sp family of transcription factors and it was shown that Cur decreased NF-κB levels by targeting Sp1, Sp3, and Sp4 transcription factors, that was dependent of the activation of reactive oxygen species (Jutooru et al., 2010). A study by Zhao et al. (2015) showed that apoptosis induced by Cur treatment results from an inhibition of Akt-signaling pathway. It consequently causes an induction of FOXO1 (forkhead box O1). A more recent study proposed that apoptosis induced by Cur is the result of activation of miR-340 and the downregulation of its target anti-protein, XIAP (X linked inhibitor of apoptosis protein) (Yang et al., 2017). The above studies demonstrate Cur's anticancer properties describe the mechanism and provide preliminary evidence for its potential use to sensitize PC cells to cytotoxic therapies.

4. Curcumin and chemotherapy combination

Gemcitabine is FDA approved and commonly used chemotherapeutic agent for a wide spectrum of cancers, including PC. Given Cur's anti-cancer properties and low level of toxicity, it was tested alongside gemcitabine to enhance the treatment's effectiveness (Kunnumakkara et al., 2007; Li et al., 2011; Yoshida et al., 2017). Lev-Ari et al. (2007) demonstrated that Cur sensitizes PC cells to gemcitabine treatment (Lev-Ari et al., 2007). Using the two different PC cell lines, P34 and PANC-1, the effect of Cur and gemcitabine (individual and in combination) was evaluated. In order to investigate whether Cur's COX-2 inhibition was involved in sensitizing gemcitabine treatment, cell lines with varying levels of COX-2 expression were tested (Lev-Ari et al., 2007). The P34 cell line had a high expression of COX-2, while PANC-1 had a low expression. Both Cur and gemcitabine increased cell death causing a dose-dependent effect in both cell lines. Annexin V-PE staining via flow cytometry revealed a pro-apoptotic effect following the treatment of Cur or gemcitabine in both cell lines. The combination treatment had the largest effect on proliferation and apoptosis in both P34 and PANC-1. There was an enhanced effect on gemcitabine-induced cell death and apoptosis with the combination treatment in the P34, but not in PANC-1. The expression of COX-2 and phosphorylated (active) extracellular signal–regulated kinase (ERK) 1/2 was also measured (Chambard et al., 2007). ERK 1/2 is known to regulate cell proliferation. In the combination treatment, there was a downregulation of both COX-2 and phospho-ERK 1/2 in P34 cells. The decrease of phospho-ERK 1/2 correlates with the reduction of cell growth in these cells. An increase of growth inhibitory/apoptotic effects in P34 attributed to Cur's inhibitory effect on COX-2. Cur's downregulation of COX-2 and phospho-ERK 1/2 may lead to the enhanced pro-apoptotic and anti-proliferative effects of gemcitabine. Cur enhances PC cell's sensitivity to gemcitabine, thus, increasing the treatment's efficacy.

5. Curcumin analogs

Cur is an attractive potential therapeutic agent for PC; however, its low bioavailability poses a challenge for clinical development (Prasad et al., 2014). For this reason, Cur analogs have been created to increase its bioavailability and improve efficiency against PC. Various Cur analogs were synthesized that demonstrate greatly enhanced anti-cancer activity compared to Cur. Cur analogs have also shown promising results with PC in pre-clinical studies. Friedman et al. (Friedman et al., 2009) synthesized and tested two analogs FLLL11 and FLLL12 with substantially greater IC50 values compared to Cur. These analogs