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Review

Use of herbal medicines and natural products: An alternative approach to overcoming the apoptotic resistance of pancreatic cancer

Lin Li, Po Sing Leung*

School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong

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ABSTRACT

Pancreatic cancer has a poor prognosis with a 5-year survival rate of <5%. It does not respond well to either chemotherapy or radiotherapy, due partly to apoptotic resistance (AR) of the cancer cells. AR has been attributed to certain genetic abnormalities or defects in apoptotic signaling pathways. In pancreatic cancer, significant mutations of K-*ras* and *p53*, constitutive activation of NFκB, over-expression of heat shock proteins (Hsp90, Hsp70), histone deacetylase (HDACs) and the activities of other proteins (COX-2, Nrf2 and bcl-2 family members) are closely linked with resistance to apoptosis and invasion. AR has also been associated with aberrant signaling of MAPK, PI3K–AKT, JAK/STAT, SHH, Notch, and Wnt/β-catenin pathways. Strategies targeting these signaling molecules and pathways provide an alternative for overcoming AR in pancreatic cancer. The use of herbal medicines or natural products (HM/NPs) alone or in combination with conventional anti-cancer agents has been shown to produce beneficial effects through actions upon multiple molecular pathways involved in AR. The current standard first-line chemotherapeutic agents for pancreatic cancer are gemcitabine (Gem) or Gem-containing combinations; however, the efficacy is dissatisfied and this limitation is largely attributed to AR. Meanwhile, emerging data have pointed to a combination of HM/NPs that may augment the sensitivity of pancreatic cancer cells to Gem. Greater understanding of how these compounds affect the molecular mechanisms of apoptosis may propel development of HM/NPs as anti-cancer agents and/or adjuvant therapies forward.

In this review, we give a critical appraisal of the use of HM/NPs alone and in combination with anti-cancer drugs. We also discuss the potential regulatory mechanisms whereby AR is involved in these protective pathways.

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Abbreviations: 5-FU, 5-fluorouracil; AR, apoptotic resistance; ASK1, apoptosis signal-regulating kinase 1; BD„ bruceine D; COX-2, cyclooxygenase-2; EGCG„ epigallocatechin-3-gallate; EGFR„ epidermal growth factor receptor; EriB, eriocalyxin B; ERK„ extracellular signal-regulated kinase; Gem, gemcitabine; GnsRh2, ginsenoside Rh2; GSK3β, glycogen synthase kinase 3β; HDAC„ histone deacetylase; HDACIs, histone deacetylase inhibitors; HM/NP s, herbal medicines and natural products; Hsp, heat shock proteins; IL, interleukin; JAK, Janus-activated kinases; JNK„ Jun N-terminal kinase; Keap, Kelch-like ECH-associated protein; MAPKs„ mitogen-activated protein kinases; MMP-9, matrix metalloproteinase 9; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphatidylinositol 3-kinase; ROS„ reactive oxygen species; SHH„ Sonic hedgehog; STAT„ signal transducers and activators of transcription; TRAIL„ tumor necrosis factor-related-apoptosis-inducing-ligand; VEGF„ vascular endothelial growth factor.

* Corresponding author at: School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Room 609A, Lo Kwee-Seong Integrated Biomedical Sciences Building, Shatin, New Territories, Hong Kong. Tel.: +852 3943 6879; fax: +852 2603 5123.
E-mail address: psleung@cuhk.edu.hk (P.S. Leung).

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1. Introduction

Pancreatic cancer is one of the deadliest cancers in the USA, where it affected about 43,920 persons in 2012 (Siegel et al., 2012). The incidence has been growing steadily in recent years. It is the fourth leading cause of cancer related death with a 5-year survival rate of less than 5% (Bayraktar et al., 2010; Siegel et al., 2011). The poor prognosis of pancreatic cancer has been attributed to its late diagnosis, limitations of surgical resection, aggressive local invasion, early metastases, and robust resistance to chemotherapy and radiotherapy (Li et al., 2010b).

Due to metastases, surgical resection is counter-indicated in over 80% of pancreatic cancer patients. Therefore, chemotherapy and radiotherapy play an important role in the treatment of this extremely aggressive disease. The standard chemotherapy approach for pancreatic cancer is treatment with the pyrimidine analog gemcitabine (Gem) alone or in combination with 5-fluorouracil (5-FU) or a platinum agent, such as cisplatin or oxaliplatin (Strimpakos et al., 2010). However, the efficacy of chemotherapy in these patients is generally poor because of the cancer cells' low sensitivity (Xia et al., 2012). The apoptotic resistance (AR) of this cancer (intrinsic or acquired) is most often the culprit for therapy failures (Long et al., 2011). Thus, potential strategies for overcoming AR have been attracting attention for the management of pancreatic cancer. Despite decades of research focused on understanding the genetic and molecular mechanisms involved in the intractability of pancreatic cancer, they are still ambiguous. Therefore, there is an urgent need to explore the molecular mechanisms of pancreatic cancer AR and further develop new effective treatments for this disease.

Gem replaced 5-FU as the standard first-line chemotherapeutic agent for locally advanced and metastatic pancreatic cancers in the 1990s. However, it offers only a 1.5-month increase in median survival time (Bayraktar et al., 2010; Li et al., 2010b). Consequently, there is a great interest in alternative therapeutic options for overcoming Gem resistance. Recent research on different cancer forms, including pancreatic cancer, has revealed that herbal medicines and natural products (HM/NPs) isolated from plants could provide additional strategies for monotherapy or combination treatments (Saad et al., 2005; Friedman et al., 2009; Liu et al., 2009; Ravindran et al., 2009; Qi et al., 2010). Indeed, over 60% of the currently used anti-cancer chemotherapeutic drugs were originally developed from natural products (Newman et al., 2003; Cragg et al., 2009). Combined with conventional chemotherapy and radiotherapy, HM/NPs can enhance therapeutic efficacy and reduce side effects (Qi et al., 2010). In this context, use of HM/NPs as an alternative approach to overcoming pancreatic cancer AR possesses great promise for development and application.

In this review, the molecular mechanisms implicated in the AR of pancreatic cancer are discussed first. Second, the present use of HM/NPs as an alternative therapeutic option for targeting these pathways is elaborated. Finally, the promising therapeutic direction of using combinations of multi-target HM/NPs with established western drugs to enhance treatment sensitivity is outlined.

2. Current therapeutic management of pancreatic cancer

Surgery is the only potential curative therapeutic approach for pancreatic cancer. However, resection rate remains low because about 80% patients are already in an advanced disease state when they are diagnosed (Xu et al., 2011). Therefore, for patients with unresectable pancreatic cancer, especially metastatic or locally advanced inoperable pancreatic cancer, chemotherapy and radiotherapy are considered the standard treatment approach (Stathis and Moore, 2010). Gem, an analog of the pyrimidine nucleotide deoxycytidine, is now the standard drug prescribed for advanced pancreatic cancer. Although Gem alone has been shown to significantly improve overall median survival time (5.6 months *vs.* 4.4 months, $p = .002$) (Burris et al., 1997), the median survival extension was merely ~1.5 months and the results are not clinically satisfactory.

Numerous second-line chemotherapeutic agents have been examined for their efficacy and toxicity in pancreatic cancer treatment, particularly in combination with Gem, including the following: 5-FU, capecitabine, pemetrexed, topoisomerase inhibitor, irinotecan and exatecan, platinum compounds (cisplatin, oxaliplatin), and taxanes (paclitaxel, docetaxel) (Bayraktar et al., 2010). Chemoradiotherapy is often used in combination with systemic chemotherapy in US oncology centers. Unfortunately, this approach has not improved survival rates significantly. Therefore, targeted therapy, gene therapy, immunotherapy, and even traditional herbal extracts (Saif, 2008; Saif et al., 2010; Ouyang et al., 2011; Liu and

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