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LETTER

Novel Drug Targets Based on Association between Inflammation and Pancreatic Ductal Adenocarcinoma

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Dear Sir,

We read with great interest the editorial published by Uomo *et al*. in the 2010 May issue of JOP. J Pancreas (Online) titled: "Inflammation and Pancreatic Ductal Adenocarcinoma: A Potential Scenario for Novel Drug Targets" [1]. There is a growing amount of evidence that inflammation plays a contributory role in the pathogenesis of cancer, including pancreatic carcinogenesis. Inflammatory states are characterized by the formation of reactive oxygen species and the induction of cell cycling for tissue growth and repair [1, 2, 3]. The initiation, promotion and expansion of tumors may be influenced by numerous components that also function in the inflammatory response. Recognized risk factors for pancreatic cancer include cigarette smoking, chronic/hereditary pancreatitis, obesity and type II diabetes. Each risk factor is linked by the fact that the inflammatory state significantly drives its pathology.

We agree with the authors that multiple links between inflammation and pancreatic adenocarcinoma has led to development of novel targeted therapy which is under evaluation both *in vivo* and *in vitro* studies to fight against pancreatic adenocarcinoma. Pancreatic cancer is one of the leading causes of cancer mortality in the United States. Current therapy for pancreatic cancer involves surgery, chemotherapy, and radiation therapy; however, the 5-year survival rate remains less than 5%. Therefore, developments of novel agents, in particular based on the pathogenesis of pancreatic adenocarcinoma are urgently indicated.

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Abbreviations PPAR: proliferator-activated receptor-gamma

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Nuclear Factor Kappa B (NF-kappa B) Activity

Few agents affecting NF-kappa B activity includes: MG132, a proteasome inhibitor [4], thymoquinone [5], fisetin, a natural flavonoid [6], sulforaphane [7], lidamycin [8], curcumin [9] and PHY906, a Chinese botanical formulation [10]. Of note characterization of sonic hedgehog as a novel NF-kappa B target gene that promotes NF-kappa B-mediated apoptosis resistance and tumor growth is potentially very important [11].

Reactive Oxygen Species (ROS)

Studies have been conducted recently on the protective effect of lycopene on oxidative stress-induced cell death of pancreatic acinar cells [12] and ascorbate-induced cytotoxicity in pancreatic cancer [13].

Proliferator-Activated Receptor-Gamma (PPAR-gamma)

Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) is a ligand-activated transcription factor that has been implicated in carcinogenesis and progression of various solid tumors, including pancreatic carcinoma [14]. The anti-tumour activity of the novel thiazolidinedione class PPAR-gamma agonist CS-7017 has recently been investigated [15]. CS-7017 inhibited the proliferation of pancreatic tumour cell line AsPC-1 *in vitro* at concentrations as low as 10 nmol/L. An elevation in the levels of adiponectin, a surrogate marker for PPAR-gamma activation was also observed in such studies [15]. These preclinical results support the evaluation of CS-7017 in a clinical trial.

Cyclooxygenase-2 (COX-2)

Several types of human tumors overexpress COX-2 but not COX-1. COX-2 produces prostaglandins that inhibit apoptosis and stimulate angiogenesis. Therefore, selective COX-2 inhibitors can reduce prostaglandin synthesis, restore apoptosis, and inhibit cancer cell proliferation. Nonselective NSAIDs such as sulindac and indomethacin inhibit not only COX-2 but COX-1, a cytoprtotective [16]. Consequently, nonselective NSAIDs can cause gastrointestinal ulceration, platelet dysfunction, and nephropathy [16]. For these reasons,

selective inhibition of COX-2 such as meloxicam, celecoxib, and rofecoxib are preferable to treat neoplastic proliferation [17]. Such agents have been evaluated in the management of pancreatic cancer in combination with radiation therapy [18] as well as with systemic chemotherapy [19, 20].

Cytokines

Cytokines, in particular tumor necrosis factor-alpha (TNF-alpha), represent an important target for a novel therapeutic target to treat pancreatic adenocarcinoma. TNFerade is an adenovector, or DNA carrier, which contains the gene for TNF-alpha, an immune system protein with potent and well-documented anti-cancer effects, for direct injection into tumors. After administration, TNFerade stimulates the production of TNF-alpha in the tumor. Clinical studies have been evaluating TNFerade for use in combination with radiation and/or chemotherapy for the treatment of pancreatic cancers [21, 22, 23].

Considering the relative chemotherapy-resistance of pancreatic adenocarcinoma to classic cytotoxic agents used alone or in multi-modality combination, efforts to evaluate both old and new drugs directed at the inflammatory mechanisms is warranted to improve the overall prognosis for patients with pancreatic adenocarcinoma.

Conflict of interest The author has no potential conflict of interest

References

1. Uomo I, Miraglia S, Pastorello M. Inflammation and pancreatic ductal adenocarcinoma: a potential scenario for novel drug targets. JOP. J Pancreas (Online) 2010; 11:199-202. [PMID 20442512]

2. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420:860-7. [PMID 12490959]

3. Farrow B, Evers BM. Inflammation and the development of pancreatic cancer. Surg Oncol 2002; 10:153-69. [PMID 12020670]

4. Matsuo Y, Sawai H, Ochi N, Yasuda A, Sakamoto M, Takahashi H, et al. Proteasome inhibitor MG132 inhibits angiogenesis in pancreatic cancer by blocking NF-kappaB activity. Dig Dis Sci 2010; 55:1167-76. [PMID 19399612]

5. Banerjee S, Kaseb AO, Wang Z, Kong D, Mohammad M, Padhye S, et al. Antitumor activity of gemcitabine and oxaliplatin is augmented by thymoquinone in pancreatic cancer. Cancer Res 2009; 69:5575-83. [PMID 19549912]

6. Murtaza I, Adhami VM, Hafeez BB, Saleem M, Mukhtar H. Fisetin, a natural flavonoid, targets chemoresistant human pancreatic cancer AsPC-1 cells through DR3-mediated inhibition of NF-kappaB. Int J Cancer 2009; 125:2465-73. [PMID 19670328]

7. Kallifatidis G, Rausch V, Baumann B, Apel A, Beckermann BM, Groth A, et al. Sulforaphane targets pancreatic tumour-initiating cells by NF-kappaB-induced antiapoptotic signalling. Gut 2009; 58:949-63. [PMID 18829980]

8. Dhillon N, Aggarwal BB, Newman RA, Wolff RA, Kunnumakkara AB, Abbruzzese JL, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. Clin Cancer Res 2008; 14:4491-9. [PMID 18628464]

9. Chen J, Wu SY, Ou-Yang ZG, Zhen YS. Synergy of gemcitabine and lidamycin associated with NF-kappaB downregulation in pancreatic carcinoma cells. Acta Pharmacol Sin 2008; 29:614-9. [PMID 18430374]

10. Saif MW, Lansigan F, Ruta S, Lamb L, Mezes M, Elligers K, et al. Phase I study of the botanical formulation PHY906 with capecitabine in advanced pancreatic and other gastrointestinal malignancies. Phytomedicine 2010; 17:161-9. [PMID 20092990]

11. Kasperczyk H, Baumann B, Debatin KM, Fulda S. Characterization of sonic hedgehog as a novel NF-kappaB target gene that promotes NF-kappaB-mediated apoptosis resistance and tumor growth in vivo. FASEB J 2009; 23:21-33. [PMID 18772349]

12. Du J, Martin SM, Levine M, Wagner BA, Buettner GR, Wang SH, et al. Mechanisms of ascorbate-induced cytotoxicity in pancreatic cancer. Clin Cancer Res 2010; 16:509-20. [PMID 20068072]

13. Seo JY, Masamune A, Shimosegawa T, Kim H. Protective effect of lycopene on oxidative stress-induced cell death of pancreatic acinar cells. Ann N Y Acad Sci 2009; 1171:570-5. [PMID 19723106]

14. Nakajima A, Tomimoto A, Fujita K, Sugiyama M, Takahashi H, Ikeda I, et al. Inhibition of peroxisome proliferator-activated receptor gamma activity suppresses pancreatic cancer cell motility. Cancer Sci 2008; 99:1892-900. [PMID 19016747]

15. Shimazaki N, Togashi N, Hanai M, Isoyama T, Wada K, Fujita T, et al. Anti-tumour activity of CS-7017, a selective peroxisome proliferator-activated receptor gamma agonist of thiazolidinedione class, in human tumour xenografts and a syngeneic tumour implant model. Eur J Cancer 2008; 44:1734-43. [PMID 18511262]

16. Harris RE, Beebe-Donk J, Doss H, Burr Doss D. Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade. Oncol Rep 2005; 13:559-83. [PMID 15756426]

17. Chen YF, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, Taylor RS. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess 2008; 12:1-278. [PMID 18405470]

18. Blanquicett C, Saif MW, Buchsbaum DJ, Eloubeidi M, Vickers SM, Chhieng DC, et al. Antitumor efficacy of capecitabine and celecoxib in irradiated and lead-shielded, contralateral human BxPC-3 pancreatic cancer xenografts: clinical implications of abscopal effects. Clin Cancer Res 2005; 11:8773-81. [PMID 16361565]

19. Dragovich T, Burris H 3rd, Loehrer P, Von Hoff DD, Chow S, Stratton S, et al. Gemcitabine plus celecoxib in patients with advanced or metastatic pancreatic adenocarcinoma: results of a phase II trial. Am J Clin Oncol 2008; 31:157-62. [PMID 18391600]

20. Lipton A, Campbell-Baird C, Witters L, Harvey H, Ali S. Phase II trial of gemcitabine, irinotecan, and celecoxib in patients with advanced pancreatic cancer. J Clin Gastroenterol 2010; 44:286-8. [PMID 20216081]

21. Chadha MK, Litwin A, Levea C, Iyer R, Yang G, Javle M, Gibbs JF. Surgical resection after TNFerade therapy for locally advanced pancreatic cancer. JOP. J Pancreas (Online) 2009; 10:535-8. [PMID 19734632]

22. Murugesan SR, King CR, Osborn R, Fairweather WR, O'Reilly EM, Thornton MO, Wei LL. Combination of human tumor necrosis factor-alpha (hTNF-alpha) gene delivery with gemcitabine is effective in models of pancreatic cancer. Cancer Gene Ther 2009; 16:841-7. [PMID 19444305]

23. Rasmussen H, Rasmussen C, Lempicki M, Durham R, Brough D, King CR, Weichselbaum R. TNFerade Biologic: preclinical toxicology of a novel adenovector with a radiation-inducible promoter, carrying the human tumor necrosis factor alpha gene. Cancer Gene Ther 2002; 9:951-7. [PMID 12386834]