PPARγ Ligand and Induction of Growth Arrest in Pancreatic Cancer Cells

AYMAN ELNEMR¹*, TETSUO OHTA¹, SACHIO FUSHIDA¹, ITASU NINOMIYA¹, GENICHI NISHIMURA¹, HIROHISA KITAGAWA¹, MASATO KAYAHARA¹, TADASHI TERADA², and KOICHI MIWA¹

Summary. Peroxisome proliferator-activated receptor γ (PPARγ), one of the nuclear receptors expressed in adipose tissue, plays an important role in adipocyte differentiation. In this study, we investigated the expression of PPARγ and its role in cellular growth in five pancreatic cancer cell lines: Capan-1, AsPC-1, BxPC-3, PANC-1, and MIA PaCa-2. All five expressed PPARγ mRNA and protein, shown respectively on reverse transcriptase-polymerase chain reaction (RT-PCR) and Western blot analysis. Clonogenic assays showed that thiazolidinedione (TZD), the parent compound of PPARγ ligands, completely inhibits colony formation of these cells at a concentration of 10μM. Moreover, treatment of these cells with 10μM TZD resulted in G₀/G₁ cell cycle arrest. In conclusion, pancreatic cancer cell lines express PPARγ, and PPARγ ligand cytostatically inhibits cell growth.

Key words. Peroxisome proliferator-activated receptor γ, Nuclear receptor, Thiazolidinedione, Pancreatic cancer, Growth arrest

Introduction

Adenocarcinoma of the pancreas is one of the most lethal malignancies. Unfortunately, more than 90% of pancreatic cancer patients present with metastatic disease or advanced local disease, precluding curative surgical resection. Chemotherapy has not resulted in a significant survival benefit [1]. On the basis of these observations, it is clear that new molecular targets are needed for the prevention and treatment of pancreatic cancer.

Peroxisome proliferator-activated receptor γ (PPARγ), a transcription factor belonging to the nuclear receptor superfamily, forms functional heterodimers with the retinoid X receptor [2]. PPARγ is of great current interest because it mediates the antidiabetic effects of several thiazolidinediones (TZDs) that are now in widespread

¹Department of Surgery II, School of Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-0934, Japan
²Department of Pathology II, School of Medicine, Tottori University, 86 Nishi-machi, Yanago, Tottori 683-8503, Japan
*e-mail: aymann1@yahoo.com
clinical use for treating type 2 diabetes [3]. Interestingly, PPARγ has a preference for polyunsaturated fatty acids and dietary components that have shown to lower the incidence of cancer in experimental animals [4], although the clinical relevance of these observations remains unclear.

Synthetic PPARγ ligands have been shown to inhibit the growth of several human tumor cell lines and, most notably, to induce growth arrest and differentiation in primary cultures of human liposarcoma and breast cancer cells in vitro and in vivo [5,6]. In contrast, there have been conflicting reports on the effects of the TZD class of PPARγ ligands in experimental colon carcinogenesis [7,8]. To our knowledge, this is the first report focusing on PPARγ expression in pancreatic cancer and induction of growth arrest by its ligand treatment.

Expression of PPARγ in Pancreatic Cancer

We initially examined the expression of PPARγ in pancreatic cancer cell lines using reverse transcriptase polymerase chain reaction (RT-PCR). Five pancreatic cancer cell lines—Capan-1, AsPC-1, BxPC-3, PANC-1, MIA PaCa-2—expressed PPARγ mRNA at significant levels (Fig. 1A). Moreover, in the surgically resected specimens PPARγ mRNA was strongly expressed in cancerous tissues compared to their normal coun-

![Fig. 1. Expression of peroxisome proliferator-activated receptor γ (PPARγ) mRNA in pancreatic cancer. A Expression of PPARγ mRNA in pancreatic cancer lines. A 236-bp band corresponds to nucleotides 545–778 of the PPARγ cDNA. B Expression of PPARγ mRNA in representative pancreatic cancer tissues of seven patients. PPARγ mRNA was strongly expressed in cancerous tissue (T) when compared to their noncancerous counterparts (N)](image)