Biochimica et Biophysica Acta 1845 (2014) 42–52

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

Type I interferon-mediated pathway interacts with peroxisome proliferator activated receptor-γ (PPAR-γ): At the cross-road of pancreatic cancer cell proliferation

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ARTICLE INFO

Article history:
Received 17 September 2013
Received in revised form 14 November 2013
Accepted 22 November 2013
Available online 1 December 2013

Keywords:
Type I interferon
PPAR-γ
Pancreatic adenocarcinoma
JAK-2/STAT-3 pathway

ABSTRACT

Pancreatic adenocarcinoma remains an unresolved therapeutic challenge because of its intrinsically refractoriness to both chemo- and radiotherapy due to the complexity of signaling and the activation of survival pathways in cancer cells. Recent studies have demonstrated that the combination of some drugs, targeting most of aberrant pathways crucial for the survival of pancreatic cancer cells may be a valid antitumor strategy for this cancer. Type I interferons (IFNs) may have a role in the pathogenesis and progression of pancreatic adenocarcinoma, but the limit of their clinical use is due to the activation of tumor resistance mechanisms, including JAK-2/STAT-3 pathway. Moreover, aberrant constitutive activation of STAT-3 proteins has been frequently detected in pancreatic adenocarcinoma. The selective targeting of these cell survival cascades could be a promising strategy in order to enhance the antitumor effects of type I IFNs. The activation of peroxisome proliferator-activated receptor γ (PPAR-γ), on the other hand, has a suppressive activity on STAT-3. In fact, PPAR-γ agonists negatively modulate STAT-3 through direct and/or indirect mechanisms in several normal and cancer models. This review provides an overview on the current knowledge about the molecular mechanisms and antitumor activity of these two promising classes of drugs for pancreatic cancer therapy. Finally, the synergistic antiproliferative activity of combined IFN-β and troglitazone treatment on pancreatic cancer cell lines, evaluated in vitro, and the consequent potential clinical applications will be discussed.

Contents

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http://dx.doi.org/10.1016/j.bbcan.2013.11.003

1. Introduction

Despite all efforts to develop effective treatments, pancreatic adenocarcinoma still represents an unresolved therapeutic challenge. It accounts for 90% of cancers of the pancreas and is the 10th most commonly diagnosed cancer but the 4th most common cause of cancer-related death among men and women (6% of all cancer-related deaths) [1]. No screening test is available for this disease and the mortality rate is so high because pancreatic cancer is usually diagnosed when it has already metastasized. Therefore, only 5% to 15% of patients are surgical candidates at the time of diagnosis [2], and, for these patients, adjuvant chemotherapy has a significant survival benefit, but the 5-year survival is only 21% [3].

Chemotherapy, alone or in combination with radiation, remains the most common treatment for patients with advanced pancreatic cancer. The gold standard is still gemcitabine administered alone or in combination with other cytotoxic agents (5-fluorouracil, capecitabine, cisplatin, oxaliplatin, nab-paclitaxel, erlotinib) [4]. However, exocrine pancreatic adenocarcinoma, within all solid tumors, is one of the most refractory to chemo- and radiotherapy, with a 5-year survival rate of about 4% and a median survival less than 6 months [5]. Possible reasons for pancreatic tumor resistance to medical therapy include the complexity of signaling and the activation of survival pathways in cancer cells.

Despite numerous trials evaluating novel therapeutic regimens for patients with advanced pancreatic adenocarcinoma, no considerable additional improvements in survival have been recently observed. This observation strongly emphasizes the need for the identification of new targets and the development of innovative therapeutic strategies.

Rationale of drug development and treatment strategies is actually aimed to counteract the main signaling pathways driving tumorigenesis. In the last two decades, there has been an increasing interest in a possible role of type I interferons (IFNs) as treatment for several cancers [6,7]. However, the antiproliferative effects of these cytokines, promoted by the Signal Transducer and Activator of Transcription protein (STAT) 1 and 2, are limited by the activation of several survival pathways [8–10]. IFN-α-induced Janus kinase (JAK)/STAT-3 represents one of the most common survival pathways activated by type I IFNs [11]. A promising way of interfering with STAT-3 signaling could be the activation of peroxisome proliferator-activated receptor-γ (PPAR-γ). In this light, it is well known that PPAR-γ agonists negatively modulate STAT-3 through direct and/or indirect mechanisms in several normal and cancer models [11].

It has been recently demonstrated a potent in vitro antitumor activity of IFN-β and troglitazone, a PPAR-γ agonist, in pancreatic cancer cell lines [12].

The present review focuses on the role of type I IFNs and PPAR-γ agonists with their related signaling pathways in pancreatic cancer, highlighting their pharmacological interaction that can be of help for future treatment modalities.

2. Type I interferon-mediated signal transduction pathways

IFNs are classified into three families: type I, type II and type III. Type I IFNs consist of different classes: IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω and IFN-τ. The classical function of type I IFNs is the protection against viral infections. However, IFNs are also involved in other biological processes: cell differentiation, control of the cell growth, immune system modulation and antitumor effect [13,14]. Indeed, these cytokines are currently used for the treatment of several diseases, such as solid and hematological malignancies, chronic viral hepatitis and multiple sclerosis [13,15].

Type I IFNs possess a common receptor complex, constituted by two chains (IFNAR-1 and IFNAR-2). IFNAR-1 is the signaling subunit and IFNAR-2 is the subunit responsible for the interaction with the ligand [16–18]. IFNAR-1 and IFNAR-2 dimerize after the interaction with the ligand [18,19], activating two intracytoplasmic receptor-associated kinases (Tyrosine kinase 2 (Tyk-2), associated with IFNAR-1, and JAK-1, associated with IFNAR-2) with consecutive tyrosine phosphorylation of IFNAR in its intracellular domain. These tyrosine phosphorylated sites represent docking elements for Src homology 2 (SH2) and phosphotyrosyl-binding domain-containing proteins, located in the membrane or in the cytoplasm [20]. Among these proteins, STATs represent a family of latent cytoplasmic transcription factors able to mediate several biological processes, including cell growth, differentiation, apoptosis, fetal development, transformation, inflammation, and immune response [21]. STATs recruited to the receptor are phosphorylated on a single tyrosine residue in the carboxyl terminal portion and released from the cytoplasmic region of the receptor subunits to form homodimers or heterodimers [22]. Once activated, IFN receptor phosphorylates and activates STAT-1 and STAT-2. These two proteins heterodimerize and bind another cytoplasmic protein, p48, forming the mature IFN-stimulated gene factor 3 (ISGF3) complex. This translocates into the nucleus and binds to IFN stimulated response elements (ISRE) or gamma-activated sequence (GAS) regulatory elements in the promoters of IFN-activated genes, thus modulating gene transcription [20]. Thus, signaling specificity via the IFN-activated JAK/STAT pathway is established by the formation of multiple complexes that activate distinct regulatory elements in the promoters of IFN-regulated genes [21,22]. Type I IFNs also modulate other non-canonical signaling pathways, like p38 mitogen-activated protein kinase (MAPK), Akt, CT10 regulator of kinase and Rat sarcoma protein (Ras) [23–25].

Through the modulation of these signaling pathways, type I IFNs exert their biological effects, such as control of protein synthesis and degradation, induction of apoptosis and cell cycle inhibition. However, the potential antitumor activity of these cytokines is limited by the activation of several cellular survival pathways that lead the tumor cells to escape from the antiproliferative mechanisms induced by IFNs. The main survival pathway activated in cancer cells treated with IFN-α is the JAK-2/STAT-3 pathway. Once activated, JAK-2 promotes recruitment to the receptor complex of the transcription factors STAT-3 and STAT-5 [26]. After its phosphorylation, STAT-3 leads to the formation of stable homodimers and heterodimers, which translocate into the nucleus where bind specific DNA promoter sequences, resulting in the transcription of genes that stimulate cell proliferation, malignant transformation and inhibit apoptosis [8,27].

Among the survival pathways induced by IFNs, nuclear factor kappa-beta (NF-kB) is activated through different mechanisms by type I IFNs and promotes cell proliferation and invasion [28,29].

Another tumor resistance mechanism induced by IFNs is the dephosphorylation of specific protein tyrosine phosphatases (PTPs) [10]. Among these proteins, two mammalian SH2-containing cytoplasmic PTPs, Shp-1 and Shp-2, once dephosphorylated, can counteract the classical IFN signaling cascade. In detail, after IFN-α binding, Shp-1 is associated to IFN-receptor and interacts with JAK-1 and Tyk-2. This complex inhibits the IFN-α-stimulated JAK/STAT pathway. On the other hand, Shp-2 promotes the activation of Extracellular signal-regulated kinases (Erk)-1/2 pathway and the expression of the platelet derived growth factor (PDGF) receptor. Moreover, it inhibits c-Jun N-terminal kinases (JNK) under cellular stress [10,30]. IFN-α can

specifically induce another SH2-domain protein, suppressor of cytokine signaling (SOCS) that inhibits the JAK/STAT-mediated pathway [31].

An additional survival mechanism activated by IFNs is represented by the overactivation of G1P3 that plays a critical role in the regulation of apoptosis. In myeloma cells, the overexpression of G1P3 induced by IFN-α2b counteracts the IFN-induced apoptotic signals and antagonizes TNF-related apoptosis-inducing ligand (TRAIL) [32].

The enhanced expression and function of the epidermal growth factor (EGF) receptor (EGF-R) in tumor cells represent a mechanism that counteracts the antitumor activity of IFN-α [33,34]. In detail, IFN-α increases the expression and signaling activity of EGF-R in epidermoid cancer cell lines [33,35,36]. After activation by EGF binding, EGF-R is phosporylated and interacts with cytoplasmic factors that activate the Ras/Raf/MAPK cascade, a main anti-apoptotic pathway counteracting the IFN-α-mediated apoptosis [33,37]. Moreover EGF/Ras pathway activates Akt/PKB, another important survival pathway [38,39].

Cyclic adenosine monophosphate (cAMP) signal represents another escape pathway from apoptosis and growth inhibition activated by IFN-α [40]. It has been described that IFN-α treatment reduced adenylate cyclase enzyme activity with a parallel decrease of intracellular cAMP levels, weakening the pro-apoptotic property of IFN. Moreover, a reduction in protein kinase A (PKA) activity and in the PKA-dependent phosphorylation of the transcription factor cAMP-response-element-binding-protein (CREB) was seen upon IFN treatment [35,41].

Finally, eukaryotic translation elongation factor 1A (eEF-1A) is included among the survival pathways activated in cancer cells during incubation with IFN-α [42]. It is involved in the first step of the protein synthesis elongation and may have an anti-apoptotic role. In H1355 cells, a human epidermoid lung cancer cell line, IFN-α increases the expression of eEF-1A directly through decrease of its ubiquitination and, consequently, of its degradation and indirectly by the activation of C-Raf, that causes eEF-1A resistance to proteasome degradation [42,43]. This survival pathway attenuates the IFN-induced apoptosis.

3. PPAR-γ signal transduction pathway

Peroxisome proliferator-activated receptors belong to a nuclear receptor family of transcription factors, represented by three isoforms, PPAR-α, PPAR-δ/β and PPAR-γ. PPAR-γ was identified as a key regulator of adipocyte differentiation and glucose metabolism that led to the development of agonists for clinical use as antidiabetic drugs. Moreover, PPAR-γ has an important role in the development and treatment of various diseases based on its anti-inflammatory, cell cycle arresting and pro-apoptotic activities [44]. Recently, a great interest for the research on PPAR-γ has been raised based on its possible implication in growth control of several tumors, suggesting that PPAR-γ can be considered as a potential target for the treatment of cancer. The human PPAR-γ gene is made of six coding exons located at chromosome 3p25.2 and generates three mRNA isoforms (PPAR-γ_1, PPAR-γ_2 and PPAR-γ_3). PPAR-γ_1 is expressed in different tissues like the large intestine, kidney, liver, skeletal muscle, prostate, breast and reproductive tracts [45]. PPAR-γ_2 is mainly expressed in adipose tissue where it exerts pleiotropic effects on metabolism, insulin sensitization and inflammation. It is also expressed in vascular endothelium, suggesting a role for this protein in vascular biology [46]. Finally PPAR-γ_3 is expressed in macrophages, large intestine and white adipose tissue. Long-chain polyunsaturated fatty acids and several eicosanoid derivatives, including a wide range of synthetic PPAR-γ ligands, are able to activate PPAR-γ. The most widely used synthetic agents belong to the thiazolidinediones (TDZs), such as ciglitazone, troglitazone, pioglitazone, rosiglitazone, LY171.833, efatutazone and rivoglitazone. Some of TDZs are clinically used in the therapy of type 2 diabetes. Interestingly, several tumors express high levels of PPAR-γ, and PPAR-γ agonists show in vitro antitumor activity [47–52]. Indeed, exposure of several tumor cells to TZDs leads to cell growth inhibition and tumor differentiation [53,54].

PPAR-γ, like other nuclear receptors, possesses a modular structure composed of three functional domains: the N-terminal, the DNA-binding, and a carboxy-terminal ligand-binding pocket domain (LBD)[55]. The LBD consists of three different arms: arm I, II and III. The hydrophilic head group of TDZs interacts with arm I, while the hydrophobic tail of the PPAR-γ ligand binds the hydrophobic arm II and arm III [56]. In particular, troglitazone is an equal mixture of four stereoisomers, arising from two asymmetric carbons located at the C-2 position of the chroman ring and the C-5 position of the thiazolidine moiety [57]. The polar head of this agonist forms five hydrogen bonds with hydrophilic pocket of the LBD. This strong interaction may explain why troglitazone is much more active than other PPAR-γ ligands [58].

PPAR-γ signaling is mediated by several distinct mechanisms, as described below.

3.1. Mechanisms of transcriptional activation

In the classical genomic action, upon ligand binding, PPAR-γ forms a heterodimer with retinoid-X receptor (RXR). The latter translocates into the nucleus and binds specific peroxisome proliferator response elements (PPRE) that are located within the promoter region of target genes [59]. PPAR-γ/RXR complex binds accessory proteins to initiate transcriptional regulation of PPRE-bearing genes. These proteins can either trigger (coactivators) or repress (corepressors) gene transcription.

In detail, after ligand binding, the corepressors are displaced and the interaction of PPAR-γ with coactivators is favored; thus, the heterodimer is free to interact with the PPRE. The coactivators possess or recruit histone acetyltransferase activity to the transcription start site. The acetylation of histone proteins modifies the transcriptional process through remodelling chromatin structure and/or acting as adapter molecules that link the nuclear receptor complex to key transcriptional machinery [60] in the promoter regions of target genes [61]. Some coactivator proteins are represented by C/EBF (CCAAT/enhancer-binding protein), CBP/P300 (cyclic adenosine monophosphate response-element binding protein), steroid receptor coactivator 1, RIP140 (receptor interacting protein 140), PPAR-γ coactivator-1, and PPAR-γ binding protein, while SMRT or NCoR are among the co-repressors [62,63].

3.2. Mechanisms of transcriptional repression

PPAR-γ inhibits transcription of several genes through different actions, such as transcriptional repression and transrepression. The first mechanism involves the binding of PPAR-γ to specific response elements in the promoter or enhancer regions of target genes, whereas in the transrepression, PPAR-γ inhibits gene transcription without the binding to PPRE [64,65]. The latter repressive function is exerted through different mechanisms: i) direct interactions between PPAR/RXR heterodimers and several activated transcription factors (e.g., STATs, activator protein 1, and NF κ-B) that prevent the heterodimer from inducing gene transcription [66]; ii) modulation of corepressors activity by blocking of corepressors clearance (through prevention of proteasomal clearance of corepressor complex after PPAR-γ sumoylation) [67]; iii) sequestration of essential coactivators (such as CREB-binding protein (CBP) and steroid coactivator receptor 1), making them unavailable for other transcriptional factors [66]; iv) regulation of kinase activity [66]. In addition, PPAR-γ represses the transcription of direct target genes in the absence of ligands (ligand-independent repression) through PPRE binding. This activity consists in the recruitment of corepressor complexes that antagonize the actions of coactivators and maintain genes in a repressed state [68,69].

3.3. PPAR-γ independent mechanisms of agonist action

Finally, PPAR-γ ligands can activate intracellular signaling by a PPAR-γ-independent mechanism, which is derived from the interaction of PPAR-γ ligands with other receptors [67]. This mechanism can be "non genomic," when cytosolic signaling pathways are involved, or "genomic," when after activation, alternative (non-PPAR) transcription factors converge on the DNA. Several PPAR-γ-independent effects have been described for PPAR-γ agonists. The PPAR-γ ligand 15-deoxy- 12,14-prostaglandin J2 (15d-PGJ2) inhibits the secretion of TNF-α and interleukin-6 in macrophages stimulated by bacterial lipopolysaccharide, and mediates anti-inflammatory effects by directly binding and inactivating I-kB kinase [70]. A novel mechanism for the PPAR-γ-independent anti-inflammatory actions of TZDs is the involvement of the JAK/STAT signaling pathways. In detail, 15d-PGJ2 and rosiglitazone are potent inducers of SOCS proteins and the overexpression of either SOCS1 or SOCS3 prevents both JAK-2 as well as STAT-3 phosphorylation in primary astrocytes [71]. In addition, TDZs exert antitumor activity interfering with multiple signaling mechanisms, independently from PPAR-γ activation, able to modulate cell cycle progression and survival of cancer cells [72].

3.4. Mechanisms of crosstalk between PPAR-γ and the mitogen-activated protein kinase (MAPK) cascades

The transcriptional activity of PPAR-γ is inhibited or regulated by several cross-talks with kinases and phosphatases. In that context, mitogen-activated protein kinase kinase (MEK)-ERK-dependent pathway can negatively regulate PPAR-γ activity through different mechanisms: i) inhibitory phosphorylation and ii) nucleo-cytoplasmic compartmentalization of PPAR-γ. After phosporylation by ERKs, PPAR-γ undergoes to ubiquitination and sumoylation with consequent repression of the PPRE transactivation and inhibition of its genomic response [73]. Mitogen and ligand stimulation also lead PPAR-γ to a rapid nuclear export mediated by MEKs. In detail, MEKs translocate into the nucleus, but are promptly exported from this location by their N-terminal nuclear export signals. Nuclear PPAR-γ interacts with MEKs and this event may favor the trafficking of this complex to the cytosol [74].

4. Antitumor effects of type I IFNs and PPAR-γ agonists in pancreatic cancer

4.1. Role of type I IFNs in pancreatic cancer

Type I IFNs regulate at the transcriptional level more than 200 genes such as NF-kB, interferon regulatory factor 1 (IRF-1), p53, STAT-1 and interleukin enhancer-binding factor 3 (NF-90) that control diverse cell processes, such as growth [75] and differentiation [76]. Most of these effects contribute to the antiproliferative activity of these cytokines by cell cycle arrest and/or apoptosis (Fig. 1) [77–90]. IFN-α and IFN-β may also mediate antitumor activity through indirect mechanisms by modulating immunomodulatory and antiangiogenic response (Fig. 1). Indeed, type I IFNs can influence immune responses through the effects on myeloid [91,92], T [93,94] and B cells [95], chemokinesis [96], and chemotaxis [97], as well as promote the acquisition of cytotoxic activity of natural killer (NK) cells [98–100]. Another interesting antitumor

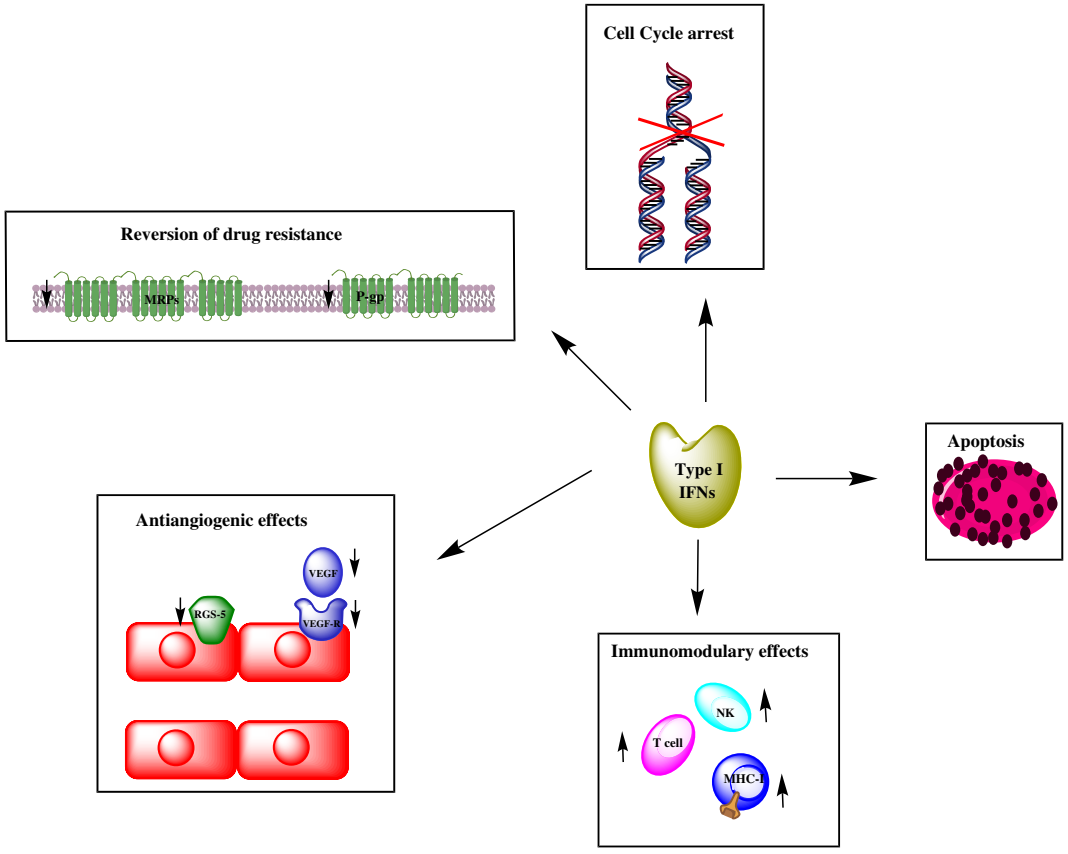

Fig. 1. Schematic illustration of molecular mechanism of type I IFN antitumor effects. Type I IFNs induce anticancer actions through different mechanisms: i) cell cycle arrest, ii) induction of apoptosis, iii) immunomodulary and iv) antiangiogenic effects, v) reversion of drug resistance. (NK, natural killer; MHC-I, major histocompatibility complex class I; MRPs, multidrug resistance-associated proteins; P-gp, P-glycoprotein; RGS-5, regulator of G protein signaling protein 5; VEGF, vascular endothelial growth factor; VEGF-R, vascular endothelial growth factor receptor; Th cell, T helper cell).

mechanism of IFNs is the antiangiogenic activity. These cytokines inhibit secretion of angiogenic factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor 2, (FGF-2), produced by tumor cells, and regulator of G-protein signaling 5 (RGS-5), which is a protein involved in angiogenic tumor vasculature [101]. The use of IFNs has been also advocated as a potential therapeutic approach to overcome multidrug resistance (MDR) (Fig. 1). Multidrug resistance-associated proteins (MRPs) are overexpressed in several aggressive tumors, such as pancreatic cancer, and a correlation of protein expression with tumor grading and impaired survival has been reported [102,103]. Interestingly, addition of IFN-α to chemotherapy regimens restores the chemosensitivity in an orthotopic mouse model of pancreatic cancer through the down-regulation of MRPs [104].

Type I IFNs may have an important role in the pathogenesis and probably in the treatment of pancreatic adenocarcinoma. Indeed, a frequent loss of chromosome arm 9p, that is the location of IFN-α and -β genes, has been observed in more than 80% of human pancreatic cancer [105]. As a result of the antiproliferative and differentiating effects of type I IFNs, the possibility that IFN-α and IFN-β genes may function as tumor suppressor genes in pancreatic cells cannot be excluded [106]. In addition, a potent antitumor activity of type I IFNs has been observed in vitro [107]. On these basis, in 2003 Picozzi et at al. published a preliminary phase II study in patients with adenocarcinoma treated with IFN-α, cisplatin and 5-fluorouracil (5-FU) together with radiation therapy [108]. These patients showed a better survival if compared to those treated with a Gastrointestinal Tumor Study Group (GITSG)—type protocol (external beam radiation therapy plus 5-FU) [108,109]. With these encouraging but preliminary outcomes, there has been an increasing interest in a possible role of IFN-α in combination with the chemo-radio-immunotherapy in the treatment for pancreatic cancer, as shown by several phase II or III trials [3,110–114]. All these studies reported a potent antitumor activity using an IFN-α-based chemo/radiation regimen in pancreatic cancer, but the price that has been paid was the occurrence of severe side effects.

Although the antitumor effects of IFN-α have been studied in detail, those of IFN-β are not well clarified. Interestingly, IFN-β is significantly more effective in vitro than IFN-α in inducing cell growth inhibition in both exocrine [107] and endocrine [115] tumors of the pancreas and adrenal cancer [116]. In these tumors, IFN-β is more potent than IFN-α in inducing both apoptosis and cell cycle arrest in late S phase. Moreover, it has been demonstrated that a high local production of IFN-β induced a strong antitumor effect on PANC02-H7 cells, a highly metastatic mouse pancreatic carcinoma cell line successfully transfected with a vector containing a murine IFN-β gene [117]. Although IFN-β is a multifunctional cytokine that binds the same receptor of IFN-α, it induces a differential response. This can be explained by the diversity between the two structures of the two cytokines that possess only 35% sequence identity. Moreover, unlike IFN-α, IFN-β is also glycosylated [118]. These differences generate different interactions, signaling and affinities for the specific receptor. In fact, IFN-β has a higher binding affinity (approximately 10-fold) than IFN-α [119] and seems to have higher synergistic interaction on tumor cell growth inhibition when combined with other antitumor agents, due to both the activation of pro-apoptotic signaling pathways [120] and the suppression of growth factors secretion [121]. Masato et al. demonstrated a stronger antitumor effect induced by cationic multilamellar liposomes containing both human IFN-β (huIFN-β) gene and gemcitabine in cultured human pancreatic cancer cells than either treatment alone [122]. Moreover, IFN-β exhibited a more potent synergistic antitumor effect with gemcitabine through IFN signal transduction even in pancreatic cancer cells with weak IFNAR2 expression [123] and a more potent radio-sensitizing effects than IFN-α [124]. Although there are no clinical trials evaluating the efficacy of IFN-β in patients with pancreatic cancer, Busch et al. described the stabilization of the disease in a patient with incomplete resection of a pancreatic cancer, treated with IFN-β in combination with gemcitabine, cisplatinum, and radiotherapy [125].

4.2. Role of PPAR-γ agonists in pancreatic cancer

Previous reports suggested that PPAR-γ exerts pro-oncogenic or antineoplastic activity in tumorigenesis and this controversial role is due to multifaceted and tissue-specific effects of this receptor. The regulation of energy homeostasis and glucose metabolism represents the main function of PPAR-γ [126]. This activity could explain the overexpression of PPAR-γ in several tumors and its increase during tumor progression. In fact, cancer cells are often deprived of oxygen, glucose, and other nutrients because of excessive demand and insufficient vascularization [127]. PPAR-γ over expression may help tumor cells to enhance cellular glucose disposal [128].

Several studies have demonstrated a clear antitumor activity of TZDs both in vitro and in vivo through different mechanisms: i) cell cycle arrest, ii) induction of apoptosis and autophagy, iii) terminal differentiation and iv) inhibition of angiogenesis and invasion (Fig. 2).

PPAR-γ activation induces cell cycle arrest in G_0/G_1 phase [129,130], decreases expression of cyclins D, E, CDK2 [131], proliferating cell nuclear antigen, retinoblastoma protein and Cdk4, and induces an increase in cyclin-dependent kinase inhibitors p21 and p27 [132].

Antineoplastic effects of PPAR-γ agonists may also be mediated by induction of apoptosis via Bcl-2 inactivation [133] and increase in Bcl-2-associated X (BAX) and phosphatase and tensin homolog (PTEN) expression [134].

Recent reports suggested that TZDs induce cell death in cancer cells through the activation of autophagy [135,136], modulated by the AKT-mammalian target of rapamycin (mTOR)-dependent signaling [137].

Increasing evidences have indicated that TZDs promote differentiation of several tumors [138]. In addition, activation of PPAR-γ inhibits FGF-2, VEGF-stimulated proliferation, urokinase plasminogen activator (uPA) and up-regulates plasminogen activator inhibitor-1 (PAI-1) [139,140] inhibiting angiogenesis and tumor invasiveness both in vitro and in vivo [141].

Several evidences suggested a potential role of PPAR-γ agonists in the treatment of pancreatic cancer. In a large cohort of primary pancreatic tumors, PPAR-γ was expressed in about 71% of pancreatic cancer tissues [49]. On the other hand, PPAR-γ was not detected in normal pancreatic acinar epithelium, and normal ductal epithelium was mostly PPAR-γ negative [49]. In addition, PPAR-γ plays a role in the regulation of epigenetic events that lead to carcinogenesis [142]. Pazienza et al. observed that in BxPC3, a pancreatic cancer cell line, rosiglitazone treatment decreases DNA methyltransferases 1 (DNMT1) expression, an important enzyme that modulates the expression of key genes involved in tumorigenesis [143]. A potent antiproliferative activity of PPAR-γ agonists has been also demonstrated in several pancreatic cancer cell lines through cell cycle arrest and induction of apoptosis [144]. Interestingly, activation of PPAR-γ promotes differentiation [145] and inhibits invasiveness of pancreatic cancer cells [146]. In addition, PPAR-γ agonists inhibit cell invasiveness in pancreatic cancer through plasminogen activator system and matrix metalloproteinases [146] and through transrepression of NF-κB and/or transforming growth factor-β (TGF-β) signaling [147,148].

The antitumor activity of PPAR-γ agonists in pancreatic cancer has been also confirmed in vivo. A study performed on Syrian golden hamsters demonstrated that pioglitazone feeding reduces the incidence and multiplicity of carcinogen-induced pancreatic tumors [149]. In another in vivo study, after rosiglitazone treatment, it was observed a decrease in both human pancreatic xenograft tumor size and microvessel density evaluated by endothelial cell staining for collagen IV [150].

5. New therapeutic direction for targeting aberrant signal transduction in pancreatic cancer treatment: can PPAR-γ agonists increase the beneficial effects of type I IFNs?

Many lines of evidence consider JAK/STAT as a pivotal point in the development, progression, and maintenance of several human tumors.

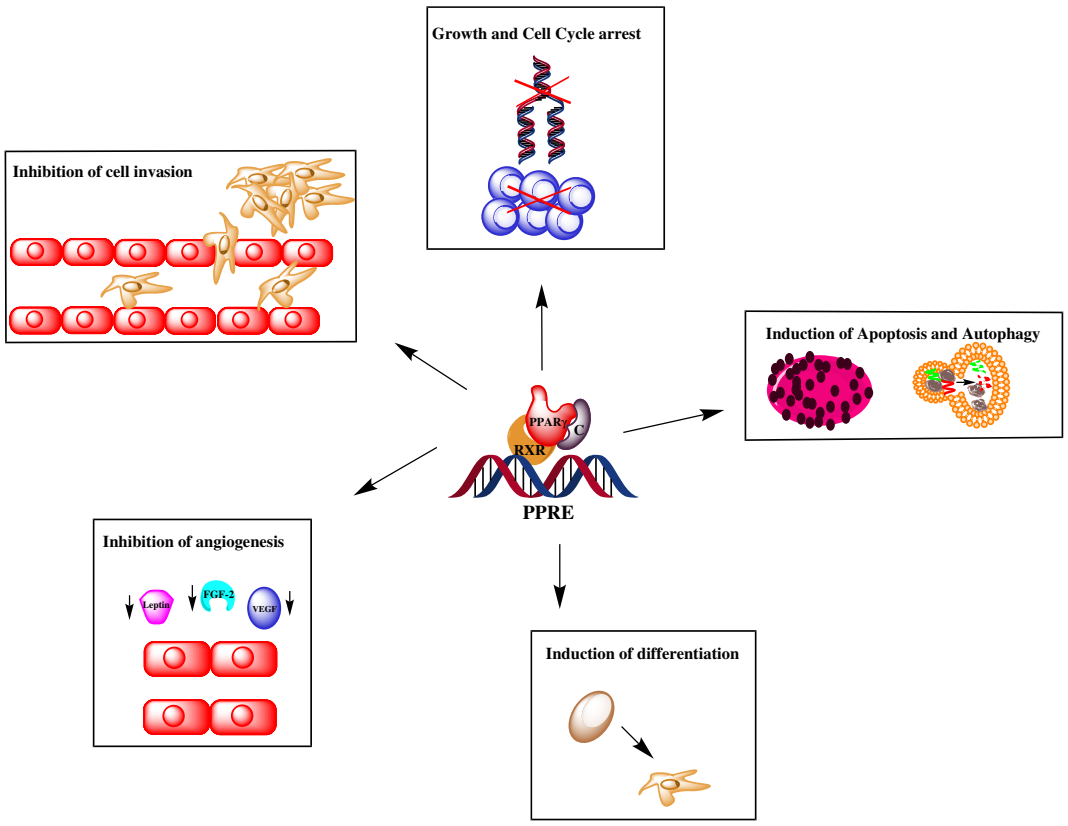

Fig. 2. Mechanisms of antitumor action of PPAR-γ. After activation, PPAR-γ exerts various antineoplastic effects like cell cycle arrest, induction of apoptosis and autophagy, terminal differentiation, inhibition of angiogenesis and of cell invasion. (C, coactivator; RXR, retinoid- X receptor; PPRE, peroxisome proliferator response element; VEGF-R, vascular endothelial growth factor receptor; FGF-2, fibroblast growth factor-2).

Within this pathway, STAT-1 and STAT-3 play opposite roles in tumorigenesis. Indeed, STAT-1 is usually considered as a tumor suppressor [151,152] and some chemotherapy agents such as fludarabine, doxorubicin or cisplatin exert their antitumor activity, at least in part, through STAT-1 activation. In contrast, STAT-3 is considered as an oncogene and its constitutive activation is reported in nearly 70% of both solid and hematological tumors [152]. STAT-3 induces the transcription of several genes involved in the regulation of critical functions, including cell differentiation, proliferation, apoptosis, angiogenesis, metastasis, and immune responses. Several studies demonstrated that STAT-3 overactivation is associated with a poor prognosis in many cancers, including pancreatic adenocarcinoma [153]. STAT-3 seems to be involved in the development of the earliest preneoplastic pancreatic lesions, acinar-to-ductal metaplasia and pancreatic intraepithelial neoplasia (PanIN) and in the progression of pancreatic ductal adenocarcinoma (PDAC) [153]. Indeed, the activation of STAT-3 stimulates cellular proliferation by promoting G1/S-phase transition and thereby contributes to the malignant phenotype of human pancreatic cancer cells [154]. Interestingly, PanIN progression is inhibited by inactivation of STAT-3 that reduces the development of pancreatic ductal adenocarcinoma (PDAC) [153].

Since STAT-3 has been validated as an anticancer target in several diseases, many therapeutic approaches have been pursued to target this protein. It has been demonstrated that activated STAT-3 antagonizes the pro-apoptotic effects of activated STAT-1 in fibroblasts and the latter may have a modulatory role in cell death signaling when STAT-3 is inhibited [155].

These results were supported by Shim et al. who also reported that the simultaneous inhibition of STAT-3 (through a JAK-2-STAT-3 inhibitor) and activation of STAT-1 (by IFN-γ) improve the tumor killing effect of JAK/STAT pathway in head and neck squamous cell carcinoma (HNSCC) [156].

Among the promises and challenges associated with the development of an anticancer strategy for targeting JAK/STAT pathway in pancreatic adenocarcinoma, a possible interaction between type I IFNs and PPAR-γ agonists has been suggested. Indeed, type I IFNs activate antitumor pathways through the phosphorylation of STATs proteins, in particular STAT-1 and STAT-2, inducing the apoptosis and cell cycle arrest in cancer cells. On the other hand, type I IFNs activate survival pathways through recruitment and activation of STAT-3, leading to cell transformation, tumor invasion and angiogenesis. In addition, Caraglia et al. demonstrated that the increased EGF-R expression and function represent another inducible survival response that protects cancer cells from IFN-induced apoptosis [33]. This receptor, together with insulin-like growth factor I (IGF-I) receptor, is overexpressed in human pancreatic cancer cells, particularly in patients with poor prognosis and in metastatic sites [157]. Moreover, both EGF and IGF-I are important upstream stimuli of STAT-3 activity [158–160] via PI3K/Akt and Ras/Raf/MEK/ERK pathway [161].

On these bases, a possible strategy to control pancreatic cancer cell proliferation and to enhance the antitumor activity of type I IFNs may be the inhibition of STAT-3 with potential clinical applications. On this light, it has been recently proposed to combine PPAR-γ agonists together with type I IFNs since transcriptional activities of STATs are modulated by PPAR-γ [160,161].

The potential combination of IFN-β plus troglitazone in pancreatic cancer was evaluated analyzing the growth inhibition induced by different concentrations of the two drugs in BxPC-3, a pancreatic cancer cell line [12]. At equitoxic concentrations, the combination of IFN-β and troglitazone synergistically inhibited cell growth. Interestingly, this

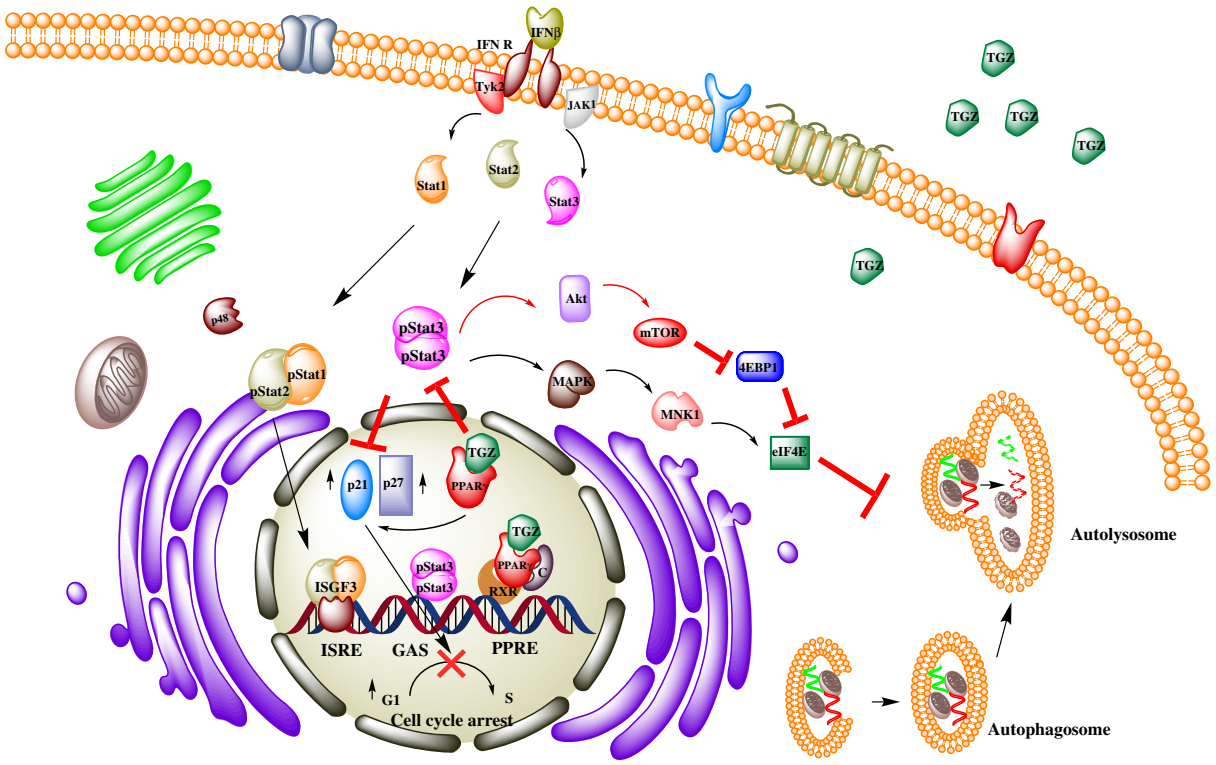

Fig. 3. Proposed mechanisms involved in the synergistic antitumor activity of IFN-β plus troglitazone (TGZ) in pancreatic cancer cells. IFN-β activates both STAT-1 and STAT-3. Phosphorylated STAT-1 stimulates the expression of cell cycle inhibitory proteins p21 and p27, but this effect is counteracted by the activation of STAT-3. In addition, STAT-3 activates the survival pathways of MAPK and AKT, inhibiting the autophagy. PPAR-γ agonist (TGZ) inhibits IFN-β-induced STAT-3 activation and directly increases the expression of both p21 and p27, potentiating the stimulatory activity of IFN-β on both cell cycle perturbations and autophagy. These effects induce a devastating antiproliferative action in pancreatic cancer cells after the combination IFN-β plus TGZ, also through the inactivation of the AKT → mTOR-dependent pathway. (→: stimulation;—|: inhibition; eIF4E: Eukaryotic translation initiation factor 4E; 4EBP1: eIF4E-binding protein 1; AKT: protein kinase B; MNK1: MAPK activated protein kinase; C, coactivator; RXR, retinoid- X receptor; PPRE, peroxisome proliferator response element; GAS: IFN-gamma-activation site; IFN β : Interferon β; IFN R: Interferon-alpha/beta receptor; ISGF3: Interferon-Stimulated Gene Factor 3 ; ISRE: interferon-stimulated response elements; JAK1: Janus kinase 1; mTOR: mammalian target of rapamycin; TGZ: Troglitazone ; TYK2 : tyrosine kinase 2; p48: cytoplasmic protein; STAT1/3: Signal Transducer and Activator of Transcription proteins 1/3).

combination induced G_1/S cell cycle arrest (Fig. 3). This event was confirmed by both the preferential cell accumulation in G_0/G_1 phase and the decrease of cell number in S phase. The transition from G_0/G_1 to S phase appeared to be directly modulated by p21 and p27, two negative cell cycle check-point regulators. Treatment with IFN-β alone increased p21 and p27 expressions through STAT-1 phosphorylation, but the concomitant IFN-β-induced STAT-3 activation attenuated the former effect. On the other hand, after the combined treatment with IFN-β plus troglitazone, the stimulation of both p21 and p27 expressions was higher than that induced by single agents, due to both a decrease in proteasome-dependent degradation and an increase in mRNA expression, especially for p27. Evaluating the effects of IFN-β and troglitazone on DNA-binding activity of STAT proteins and of PPAR-γ, it was observed that the synergistic combination highly enhanced the binding of both STAT-1 related complexes and PPAR-γ to specific DNA responsive elements.

In addition, it was analyzed the effect of the combination on the pro-survival pathways dependent from IFN-β-mediated STAT-3 activation. Previous reports demonstrated that IFN-α activated an anti-apoptotic survival pathway, dependent from Ras/Raf/MAPK-mediated pathway in human epidermoid cancer cells and the inhibition of this signaling potentiated the anti-tumor activity of this cytokine [27,33,158,162,163]. In BxPC-3 cells, IFN-β increased MAPK phosphorylation that was dependent from STAT-3 activation, triggering a survival pathway that limited the antitumor effects of IFN-β. This effect was counteracted by troglitazone through STAT-3 inhibition.

The synergistic combination of IFN-β plus troglitazone appeared to be also dependent by the triggering of an autophagic program [137] (Fig. 3). In fact, pancreatic cancer cells did not show significant changes after treatment with IFN-β alone, but after incubation with troglitazone, many cells showed the presence of autophagolysosomes, typical structures present in autophagic cells. This phenomenon was extremely potentiated when the cells were treated with the combination of IFN-β plus troglitazone and it was regulated by AKT-mTOR signaling pathway [137]. The activation of mTOR phosphorylates two major downstream components, p70S6K and eIF4E-binding protein 1 (4EBP1). 4EBP1 primarily regulates cap-dependent translation by binding and inactivating eIF4E, an initiation factor, which mediates the initiation of translation [164]. Phosphorylation of 4EBP1 releases eIF4E and subsequent activates the eIF4G scaffolding protein to promote translation. Single agents significantly reduced 4EBP1 phosphorylation without any significant changes in eIF4E phosphorylation; on the other hand, the combination of IFN-β plus troglitazone highly decreased the phosphorylation of eIF4E and of its inhibitor, 4EBP1, decreasing translation process and cell growth and bringing the cells to death by autophagy (Fig. 3).

6. Conclusions

The type I IFN-dependent signal transduction pathway can play an important and physiological role in the control of both cell proliferation and progression of pancreatic cancer. However, the role of agents acting on this pathway is greatly limited by the activation of several escape mechanisms over-expressed in tumor cells. It has been demonstrated that the PPAR-γ-dependent pathway, involved in both the regulation of cellular metabolism and tumor proliferation, interacts with the type I IFN-mediated signaling decreasing some relevant pro-survival escape mechanisms induced by these cytokines. The combination of IFN-β

plus troglitazone modulates the molecular signaling pathway of pancreatic cancer, inducing both cell cycle perturbations and autophagic cell death. The antitumor synergistic interaction between the two agents is due to the counteraction of the IFN-β-induced activation of STAT-3, MAPK and AKT and to an increase in the binding of both STAT-1 related complexes and PPAR-γ with specific DNA responsive elements. On the basis of this statement, other STAT-3 specific inhibitors recently developed [165], such as G quartet oligodeoxynucleotides, small molecules (targeting the STAT-3 SH2 domain) and decoy oligodeoxynucleotides (targeting STAT-3 DNA binding domain), may synergistically potentiate the antitumor activity of IFN-β. In addition, given the ability of type I IFNs to overcome drug resistance, we cannot exclude a potent antitumor effect combining IFN-β and PPAR-γ agonists with currently used cytotoxic drugs in pancreatic cancer such as gemcitabine. Future in vivo preclinical and clinical studies are mandatory to evaluate these potential effects in patients with pancreatic cancer, in order to open a new scenario in the targeted therapy of this devastating tumor.

Acknowledgements

This work was partially supported by the Italian Ministry of Education, Research and University (FIRB RBAP11884M) and MC was supported by the Italian Ministry of Education, Research and University (PRIN 2009).

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