Role of p53 family isoforms in enhancing aggressiveness and chemoresistance in pancreatic cancer (Review)

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Abstract. Pancreatic cancer remains one of the leading causes of cancer-related mortality worldwide. The role of p53 family isoforms in the pathogenesis of human cancer has been under the radar for decades, mainly due to the significant structural homology of p63 and p73 genes with the notorious p53 gene. Both p63 and p73 have two main isoforms, transactivating (TA) and deltaN (DN), each of which has been studied in normal and cancer cells. Although their role in cancer remains elusive and is tissue-specific, the manner in which they act in pancreatic cancer is evident. As for p53, the mechanism of its gain-of-function activities in pancreatic cancer is now better understood. In this review, the role of each gene and their isoforms is discussed, as well as the possible therapeutic agents for pancreatic cancer. Currently, the science revolving around p53 family isoforms focuses on their specific roles. Thus, we propose that future research be directed at studying the interaction between the isoforms, as well as accelerating the assessment of potential therapeutic agents.

Contents

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1. Introduction

Worldwide, pancreatic cancer is the 7th most common cause of cancer-related mortality, resulting in approximately 432,000 deaths per year, according to the 2018 GLOBOCAN study (1). In Western countries alone, the mortality rate associated with pancreatic cancer is ranked 4th and is projected to be ranked 2nd by 2030 (1,2). In the United States, 82% of pancreatic cancer cases lead to death (3). Among the different types of pancreatic cancers, pancreatic ductal adenocarcinoma (PDAC) encompasses 90-95% of all cases (4,5). According to the American Cancer Society, a patient with stage IIA pancreatic cancer has a 5-year survival rate of approximately 5% (6). These statistics indicate an alarming increase in the incidence of and mortality associated with pancreatic cancer. The poor prognosis of patients with pancreatic cancer is due to a number of reasons, including late-stage detection, a lack of sensitive and specific markers, as well as ineffective imaging in the early stages (4,7).

p53 family isoform proteins include p53, p63 and p73, all of which are evolutionarily conserved in humans and other animals. In fact, the origins of p63 seems to go further than the other two proteins (8-10). In cancer research, p53 is known to be the 'guardian of the genome' with anti-proliferative properties that prevent the growth of cancer. In 1997, the discovery of p63 and p73 genes, both of which encode for p53-like sequence specific transcription factors with similar functions, attracted scientists to investigate their role in various types of cancer (11-15).

p63 and p73 have the potential to transactivate target genes of p53, including BAX, NOXA and PUMA, which are responsible for cell death, p21^{WAF1}, responsible for cell cycle arrest and cellular senescence, and 14-3-3σ, which is pivotal in cell cycle arrest (8,12). The transactivating (TA) isoforms of p63 and p73 transactivate p53-target genes in response to anti-cancer drugs with pro-apoptotic functions, while the NH_2-terminally-truncated deltaN (DN) isoforms exert a dominant-negative behaviour against TA, and hence, are known to be pro-oncogenic (16). It should be noted that p53-dependent cell death requires the assistance of TAp73 and/or TAp63, whereas TAp73/TAp63-dependent cell death following DNA damage occurs without the need for p53 (17).

With their controversial roles in cancer, interest in the p53 family isoforms has intensified over the past decade. Notably,

research into p53 mutations in PDAC progression has established a platform for exploration of their various interactions with p63 and p73 (16,17). It is becoming increasingly clear that the aggressive and chemoresistant traits of PDAC may not be entirely elucidated by p53-driven mechanisms alone, but may implicate specific isoforms of the p53 family (18-20). Thus, this review discusses the role of the p53 family isoforms in pancreatic cancer, with a perspective on factors conferring cancer aggressiveness and chemoresistance.

2. Structure of p53 family isoforms

Structural similarity in proteins can be an indication of the functional similarity of these proteins and p53 family isoforms are no exception (21,22) (Fig. 1). Isoforms of the p53 family have a similar build, with an N-terminal transactivation domain (TAD) together with a proline-rich domain (PR), a central, highly similar DNA-binding domain (DBD), followed by a C-terminal tetramerisation/oligomerisation domain (OD). p63 and p73 contain an additional sterile alpha motif (SAM) domain and a transcription-inhibition domain (TID), which are absent in p53 (23-28). Unlike p53, p63 and p73 exist in distinct functional isoforms, those containing a TAD and those without (13,28). Functionally, TAD seems to be involved in DNA editing and repair pathways, as well as cellular senescence (29); the SAM domain is known to be involved in protein-protein interaction, as well as in the stabilisation of p63 and p73 proteins (24,29,30); thus, it has been suggested that p63 and p73 are more stable than p53 due to the presence of the SAM domain (31).

3. Role of p53 mutations in pancreatic cancer

The p53 gene codes for a nuclear transcription factor that responds to genotoxic stress. Strong genotoxic stress activates p53 and promotes cell cycle arrest, cellular senescence and apoptosis, while mild genotoxic stress can activate pathways responsible for repair mechanisms (17,20,32,33). On its own, p53 has 12 different isoforms with similar or unique functions, as a result of alternate splicing, the presence of diverse transcription promoters, as well as multiple translation initiation sites (32,34,35).

In human cancer, p53 inactivation by mutation occurs in >50% of cases, and therefore, it is known to be the most common genetic alteration (36,37). These mutations commonly occur within the DBD, resulting in the loss of p53 functions (38,39). In spite of this, the expression of mutant p53 remains in cancerous cells, which is suggestive of gain-of-function activities. In fact, cancers with the expression of mutant p53 are known to develop more aggressive tumours with an earlier onset, in comparison with cancers that are p53-null (9,35,40,41). The missense mutations, R248H, R273H and R175H, are p53 mutations with the highest frequencies in human cancer (35,40,42,43). Certain mutations result in the loss-of-function of remaining wild-type p53 (dominant-negative effect), while others are known to exert a dominant-negative effect on other tumour suppressors, such as TAp73 (35,44-52).

In pancreatic cancer, p53 is mutated in 75% of cases (53). Often, p53 mutations can be observed in PDAC, followed by adenosquamous carcinoma of the pancreas (54). In pancreatic neuroendocrine neoplasms, mutant p53 expression is uncommon (55). The sustained expression of mutant p53 seems to be associated with the aggressiveness of pancreatic cancer tumours (56). In the study by Morton *et al* (2010), mice harbouring pancreatic cancer cells with mutant *KRAS* and p53 exhibited increased metastases compared to identical mice harbouring the p53-null allele (57).

Mechanisms of p53 gain-of-function mutations. Gain-of-function activities of mutant p53 are responsible for the enhanced tumourigenicity of pancreatic cancer. This was first proven by Wolf *et al* (1984) through the transfection of mutant p53 into p53-null tumour cells (58). A number of studies have since demonstrated specific p53 gain-of-function activities, such as metabolic changes, migration, promoting cell proliferation, metastasis anti-apoptosis, invasion and angiogenesis (59-62). Studies on MiaPaca-2 pancreatic cancer cell lines, which contain the R273H mutation of p53, have demonstrated that this mutation is responsible for increased proliferation, increased colony formation and drug resistance (36,57,63-65). Platelet-derived growth factor receptor β (PDGFRβ) has been identified as a downstream mediator of mutant p53 in MiaPaca-2 and BxPC-3 pancreatic cancer cell lines, as well as in murine pancreatic cancer models. This PDGFRβ-mutant p53 axis is believed to increase pancreatic cancer cell growth (56). Mutant p53 has also been known to manipulate the pancreatic cell autophagy mechanism, resulting in increased nutrient uptake and a higher growth rate (66).

The mechanisms though which the different p53 hotspot mutations exhibit the gain-of-function properties are diverse. Family isoforms of p53 are structurally similar to p53, particularly in the DNA-binding domain, which allows a p53 target genes to interact with p63 and p73 to mediate responses, such as cell cycle arrest, cellular responses to stress and apoptosis. A subset of p53 hotspot mutations are capable of inactivating p63 and p73 by forming complexes with them. These interactions, which become possible through the conformational changes in the DNA-binding domain of mutant p53, result in gain-of-function properties, such as metastasis, invasion, migration and chemoresistance (21,48,67).

Another mechanism involves physical interaction between mutant p53 and transcription factors, such as NF-Y to mediate target gene expression by altering cell cycle regulation, since the DNA binding sequence of NF-Y is present in the regulatory region of genes involved in the cell cycle (68), as well as interactions with other transcription factors, such as E2F transcription factor 1 (E2F1), vitamin D receptor and nuclear factor (NF)-κB (69). Zhang *et al* (2013) (62), through their *in vivo* and *in vitro* evaluation of mutant p53 knockin mice, discovered that mutant p53 is capable of driving the Warburg effect. This phenomenon is likely driven by the activation of ROCK signalling, which promotes the translocation of GLUT1 to the plasma membrane (62).

Mutant p53 is also known to enhance tumourigenicity and genomic instability by forming complexes with proteins, such as MRE11 (R175H), a DNA nuclease (70), and topoisomerase 1 (R273H), which is responsible for maintaining DNA topology (71). The mutant p53-ATM complex is responsible for inactivating DNA damage responses and leads to chromosomal translocations and cell cycle arrest (in the case
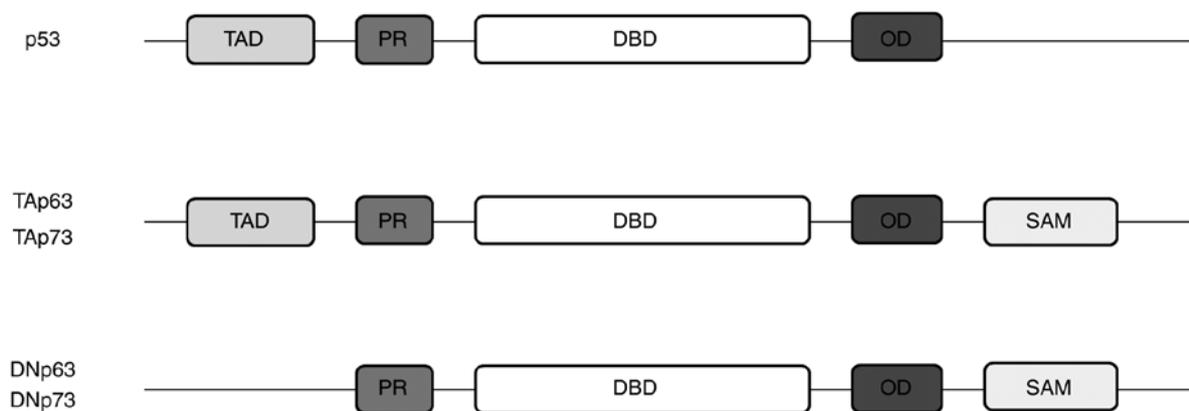
Figure 1. A comparison between genetic structures of p53 family isoforms. TA, transactivating domain; DN, deltaN domain.

of R273H mutation) (72). Brosh and Rotter (2009) demonstrated that mutant p53 is capable of up- or downregulating various genes involved in tumourigenesis, such as NF-κB2, vascular endothelial growth factor receptor (VEGFR), Myc, Fos, insulin-like growth factor 2 (IGF2), insulin like growth factor 1 receptor (IGF1R) and early growth response protein 1 (EGR1) (61). This is possible due to the DNA-binding ability of mutant p53 in a DNA structure-selective mode. It has a high affinity for the AT-rich regions and is shown to bind selectively with high affinity B conformation DNA (73,74).

Interaction with miRNA is another mechanism through which mutant p53 exerts its effect, by either inducing or repressing its functions. MicroRNA (miR)-155, which has been shown to repress zinc finger protein 652 (ZNF652), and miR-27a, which has shown to repress EGFR, are both suppressed by mutant p53. Through the repression of EGFR, mutant p53 is capable of stimulating cell proliferation and tumourigenesis by promoting sustained EGFR-induced ERK1/2 activation (75,76). Table I summarises the various mechanisms for mutant p53 gain-of-function.

4. Role of p63 isoforms in pancreatic cancer

The p63 protein consists of at least six variants, three of which contain a TA domain, and the remaining without (DN domain) (8). These isoforms regulate a wide range of target genes with opposing regulatory effects. However, their role in cancer remains ambiguous (77). The view that TAp63 is a tumour suppressor, while DNp63 acts as an oncogene is not always applicable (51,77). For instance, the study by Flores *et al* (2005) concluded that p63 heterogeneity leads to the development of spontaneous tumours (78), while Keyes *et al* (2006) came to the opposite conclusion (79). The TA and DN isoforms of p63 play various roles in normal cells, as well as in cancerous ones; TAp63 is responsible for glycolysis through liver kinase B1 (LKB1) protein kinase regulation, fatty acid oxidation, insulin secretion, pro-oxidant response, as well as female germ cell preservation (80-84).

In cancer, TAp63 is known to prevent metastases by cell apoptosis and senescence (51,78). Previously, the loss of p63 as a whole was shown to be associated with an accelerated tumour growth and increased invasiveness (85,86). Current research has even extended this finding to prove that it is the

loss or inactivation of TAp63 coupled with a p53 mutation, that leads to enhanced tumourigenicity through transforming growth factor (TGF)-β-induced pathways and the alteration of DNA repair genes (87-89). These findings regarding the function of TAp63 and the consequences of its loss or inactivation have also been proven in pancreatic cancer (88). In fact, TAp63 has a low expression in T3M4, BxPC3, COLO-357, ASPC-1 and PANC-1 pancreatic cancer cell lines, which supports the anticancer properties of TAp63 (18).

The interaction between p63 and p53 plays an important role in cancer progression, and both wild-type p53 and mutant p53 are able to interact with p63 protein (48). Mutant p53 displays a stronger dominant-negative behaviour against TAp63 in comparison with wild-type p53, resulting in the impairment of p63 transactivational target genes (20,35,49). This mechanism has been associated with enhanced cell invasion and metastases in various types of cancer, particularly breast cancer (87,90,91).

The role of DNp63 includes maintaining stem and progenitor cells in stratified and glandular epithelial tissues, as well as glycolysis and antioxidant defence (92-95). As the most abundant p63 isoform, the overexpression of DNp63 in head and neck cancer, non-small cell lung cancer and bladder cancer suggests its tumour survival properties (96-99). In spite of this, there are studies that have demonstrated a low expression of DNp63 in breast and prostate adenocarcinoma, as well as in urothelial carcinoma (97,100). This could indicate the suppressive effect of DNp63 in certain types of cancer, alluding to the paradoxical role of p63. According to Yang *et al* (2011), DNp63 overexpression is limited to squamous cell carcinoma in which it counteracts p53-mediated tumour suppressive activities (101). In pancreatic cancer, DNp63 is the predominant isoform, with its overexpression being limited to squamous differentiation (18,102). In BxPC-3, COLO-357 and T3M4 pancreatic cancer cell lines, DNp63 expression is elevated, which suggests its cancer-enhancing properties (18).

Runt-related transcription factor 2 (RUNX2) is a nuclear transcription factor generally associated with osteoblast differentiation and bone formation (103,104). In tumours, RUNX2 overexpression has been observed in breast, prostate, gastric cancer and melanoma, as well as in acute myeloid leukaemia (105-110) through target genes responsible for angiogenesis, invasiveness and metastasis, such as VEGF,

Table I. Mechanisms of major missense hotspot p53 mutations.

Author/(Refs.), year	Mechanism	Examples
Liu *et al* (171), 2014	Interaction with p53 family isoforms	R248W
Stindt *et al* (172), 2015		R175H
Oren and Rotter (52), 2010	Binding to DNA to alter gene expression	R248W
Ludes-Meyers *et al* (173), 1996		R175H
Fiorini *et al* (69), 2015		R273H
Weisz *et al* (174), 2004		
Scian *et al* (175), 2005		
Song *et al* (70), 2007	Formation of complexes with proteins	R175H
Liu *et al* (72), 2010		R273H
Di Agostino *et al* (68), 2006	Binding to transcription factors	R273H
Strano *et al* (176), 2007	Regulation of miRNA	R273H
Wang *et al* (177), 2017		

secreted phosphoprotein 1 (Spp1), matrix metalloproteinase (MMP)9 and MMP13 (107,111). As regards pancreatic cancer, Kayed *et al* discovered the pro-oncogenic role of RUNX2 overexpression and its effect on the tumour micro-environment (109). RUNX2 is responsible for resistance to gemcitabine (GEM) by attenuating p53-dependent cell death, and the silencing of RUNX2 using siRNA has been shown to significantly increase GEM sensitivity, irrespective of the p53 status (20,112-114).

One reason for the strong expression of mutant p53 in pancreatic cancer is the presence of histone deacetylase (HDAC) 1 and 2 (115). Therefore, HDAC inhibitors are under investigation as potential anticancer drugs, of which SAHA, which also affects RUNX2 levels, has recently attracted attention (116,117). MiaPaCa-2, a pancreatic cancer cell line, contains a p53 R248W mutation. As previously demonstrated, upon treatment with SAHA, although the TAp63, γH2A histone family member X (γH2AX), p21, phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1, also known as NOXA) and poly(ADP-ribose) polymerase (PARP) cleavage levels increased, and mutant p53, RUNX and TAp73 were downregulated, the response drug response was relatively poor. However, when p53 was knocked down in MiaPaCa-2 cells, the further downregulation of RUNX2 and upregulation of TAp63 were found to lead to an enhanced sensitivity to SAHA. Similarly, the knockdown of RUNX2 led to the further downregulation of mutant p53 and the upregulation of TAp63 (118). These findings by Ogata *et al* (118) provide evidence of a regulatory axis involving RUNX2, mutant p53 and TAp63.

RUNX2 knockdown in AsPC-1 p53-null pancreatic cancer cells has been shown to increase GEM sensitivity through TAp-63-dependent cell death pathway activation (113). In PANC-1 pancreatic cancer cells with R273H p53 mutation, RUNX2 depletion mediates TAp63 induction (119). This has been achieved by the exposure of PANC-1 cells to GEM, after which γH2aX was increased as a sign of DNA damage, and p73^{KIP1} and phosphor-histone H3 at Ser-10 were reduced as a sign of decreased mitosis. In addition, PARP cleavage was detected at negligible levels. These data suggest that GEM treatment suppresses the cell proliferation rate, but does not effectively promote cell death. At the same time, TAp63 target gene products p21^{WAF1} and NOXA are upregulated (119,120). Specific to TAp73, the E2F-1 transcriptional activator is also upregulated (119,121,122). Ozaki *et al* (119) then examined the effect of GEM after mutant p53 was knocked down. The depletion of mutant p53 in pancreatic cancer cell lines with homozygous p53 mutation was not sufficient to enhance the cytotoxic effect of GEM therapy. However, when RUNX2 was knocked down, the cytotoxic effect of GEM was improved in both p53-proficient and deficient pancreatic cancer cells by enhancing TAp63 target genes (p21^{WAF1} and NOXA), but not through TAp73. This was proved by transfecting PANC-1 cells with TAp63α plasmids, which exhibited an enhanced cell cycle arrest and/or cell death (119).

miR-301a plays a role in pancreatic cancer hypoxia-induced chemoresistance by targeting p63 and phosphatase and tensin homolog (PTEN) in pancreatic cancer cells (123,124). miR-301a has been reported to be upregulated in pancreatic cancer in comparison with the normal pancreas and/or pancreatitis (125). Therefore, miR-301a has the potential to be an independent prognostic marker for pancreatic cancer (126). In various tumours, hypoxia or low oxygen tension is associated with chemoresistance (127) by the upregulation of hypoxia-inducible factors (HIFs) in tumour cells (128,129). In pancreatic cancer, a few of these factors have been identified, including glucose transporter type 1 (GLUT1), ATP binding cassette subfamily B member 1 (ABCB1) and ATP binding cassette subfamily G member 2 (ABCG2), all of which are HIF-1 target genes (130-132).

miR-301a expression is increased in an NF-κB-independent manner due to hypoxia. The accumulation of miR-301a leads to a decrease in the TAp63 and PTEN protein levels, and an increase in the phosphorylation of Akt and HIF-1 factors. Notably, the overexpression of TAp63 in hypoxic pancreatic cancer cells leads to reduced cell viability, whereas under normoxic conditions, this effect is not significant. This finding

is suggestive that a reduction in TAp63 contributes to hypoxia-induced gemcitabine resistance in pancreatic cancer cells. All in all, Luo *et al* suggested that hypoxia reduced TAp63 and PTEN through the upregulation of miR-301a, which in turn promoted the accumulation of HIF-1a factors and the phosphorylation of Akt, leading to gemcitabine resistance (124).

The ability of DNp63 to regulate cell adhesion in mammary epithelial cells and keratinocytes suggest its role as an oncogene (133). This was also shown in pancreatic cancer by a direct association between DNp63α and β1-integrin, an extracellular matrix component that plays a critical role in determining the invasive phenotype of PDAC (134). Upon the upregulation of DNp63α in PANC-1 cells, increased colony formation and proliferation was observed through an increase in EGFR signalling and its downstream kinases, extracellular-signal-regulated kinase (ERK), Akt and c-Jun N-terminal kinase (JNK) (134). These outcomes, however, have not been consistently evident in other types of pancreatic cancer cells.

5. Role of p73 isoforms in pancreatic cancer

Similar to p53, p73 induces apoptosis by transactivating p53-regulated promoters, as well as other p73 target genes, such as p53 upregulated modulator of apoptosis (PUMA), Bax and GRAM domain containing 4 (GRAMD4), which induce apoptosis by acting on the cell mitochondria and cytoplasm (27,47,135-137). Researchers remain divided as to its role in angiogenesis; some studies have suggested that TAp73 exerts a suppressive effect (138,140), whilst others have demonstrated that it is pro-angiogenic (140-142). DNp73 has been constantly shown to be pro-angiogenic (139-142).

As the predominant isoform of p73, the loss of TAp73 in various cell lines or mouse models has been associated with spontaneous tumour development due to an enhanced genomic instability and the inability of DNA repair mechanisms to be activated (89,143,144). By contrast, a recent study suggested the ability of TAp73 to indirectly induce the expression of interleukin (IL)-1β in lung cancer cell lines, which is suggestive of its tumour-enhancing properties (145). As regards the tumour-suppressive properties of TAp73, a mechanism involving miRNA induction has been identified; these miRNAs, such as miR-3158, inhibit cell migration through epithelial-mesenchymal transition (EMT) and exhibit anti-invasive properties in p53-mutant cancer cell lines (146,147).

In the progression of cancer, the interaction between mutant p53 and p73 plays an important role. Mutant p53 has the ability to co-precipitate and interact with p73, resulting in a dominant-negative effect, which inhibits p73 activities (47,48). It is also clear that certain p53 mutations. such as R175H, which have a high frequency in pancreatic cancer cases (43), exhibit a stronger binding with p73 in comparison with R273H mutation (36,48).

TGF-β plays a tumour suppressive role in pancreatic cancer mediated by SMAD4 (148). The absence of TAp73 disables the SMAD4 dependent TGF-β pathway in pancreatic cancer. In the study by Thakur *et al* (19), TAp73-positive and -negative cell lines were developed from mouse models of pancreatic cancer. In TAp73-deficient cells, which were also p53-null, an increase in EMT markers, such as N-cadherin and vimentin, as well as a reduction in the TGF-β inhibitor, biglycan (BGN), and SMAD4, were suggestive of the role of TAp73 in limiting EMT progression (19).

6. Therapeutic targets of pancreatic cancer

GEM is a nucleoside analogue and a standard chemotherapeutic drug for pancreatic cancer (149). Although the primary action of GEM is the inhibition of DNA synthesis by the incorporation of gemcitabine diphosphate into DNA (150), it has a secondary effect of activating p53 target genes by binding to DNA and terminating DNA elongation, leading to apoptosis (151-153). GEM itself requires phosphorylation in order to become active and cause cytotoxicity (113). Resistance against GEM is increasing, particularly in pancreatic cancer cell lines with p53 mutation, such as MiaPacCa-2, or cell lines that are null-p53, such as AsPC-1 and cell lines, such as SW1990 that are p53 proficient are yet to exhibit GEM resistance (20,113,149).

Numerous studies have examined mechanisms through which to restore GEM sensitivity in pancreatic cancer. In p53-null pancreatic cancer cell lines, such as AsPC-1, the knockdown and silencing of RUNX2 has been shown to enhance GEM sensitivity through TAp73 and TAp63 pathways which activates p21 and NOXA genes (20,113).

Mouse double minute 2 (MDM2), Itch and neural precursor cell-expressed developmentally downregulated gene 4 (NEDD4) are ubiquitin ligase proteins that are known to suppress p73 in pancreatic cancer (149,154,155), and hence, their expression exhibits enhanced resistance to GEM therapy (156). Targeting these proteins could enhance GEM sensitivity in pancreatic cancer. MI-319 is an siRNA that, in combination with cisplatin, is known to inhibit MDM2 and therefore activate p73 (157). In pancreatic cell lines and xenograft models with p53 mutation, the knockdown of Itch by anti-Itch shRNA transduction coupled with GEM therapy has demonstrated improved sensitivity to GEM (149). Similarly, curcumin and curcumin difluorinated have been identified as an anticancer agents that inhibit NEDD4 and promote p73 activities, and hence improve the response to GEM therapy (155,158). Apart from these three proteins, AKT PI3K protein kinase is known to stabilise mutant p53 protein, and therefore, its inhibition is related to an enhanced effectiveness of cancer therapies (159). Although the effect of AKT/PI3K has not been documented for pancreatic cancer, it is a potential therapeutic target for future research in this area.

Apart from GEM, imatinib, a chemotherapeutic drug most commonly used for chronic myeloid leukaemia, is a potential treatment for pancreatic cancer with mutant p53. It targets the PDGFRβ pathway, which is constitutively activated by mutant p53 resulting in uncontrollable cell growth (56).

In terms of gene therapy, knocking down the DN isoform of p63 is promising target for pancreatic cancer therapy (18). In a study using mouse models of pancreatic cancer, the shRNA-mediated knockdown of DNp63 was shown to lead to a decrease in tumour volume compared to identical mice carrying non-targeting shRNA (160). Table II summarises the strategies used to inhibit various therapeutic targets in pancreatic cancer.

Table II. Therapeutic targets that cause resistance to gemcitabine or confer tumour tumour-enhancing properties and strategies to inhibit these targets.

Author/(Refs.), year	Therapeutic target	Mechanism of resistance/tumourigenicity	Method of inhibition
Sugimoto *et al* (113), 2015 Nakamura *et al* (20), 2016	RUNX2	Inhibits TAp73 and TAp63 pathways	siRNA-mediated knockdown
Azmi *et al* (157), 2010 Yang *et al* (156), 2017	MDM2	Suppresses p73 pathways	Inhibition by MI-319 coupled with cisplatin
de la Fuente *et al* (149), 2015	ITCH	Suppresses p73 pathways	Anti-Itch shRNA knockdown
Azmi *et al* (158), 2011 Su *et al* (155), 2017	NEDD4	Suppresses p73 pathways	Inhibition by curcumin and curcumin difluorinated
Hamilton *et al* (159), 2014	AKT PI3K	Stabilises mutant p53 protein	AKT inhibition by MK-2206
Weissmueller *et al* (56), 2014	DNp63	Promotes cell growth	Anti-DNp63 shRNA knockdown
Urist *et al* (85), 2002 Bid *et al* (160), 2014	PDGFRβ	Activated by mutant p53 and promotes cell growth	Inhibition by imatinib

RUNX, runt-related transcription factor 2; MDM2, mouse double minute 2; NEDD4, neural precursor cell-expressed developmentally down-regulated gene 4; AKT PI3K, phosphatidylinositol-3-kinase and proteinase kinase B; PDGFRβ, platelet derived growth factor receptor β.

Table III. drugs involved in p53-mediated therapy for pancreatic cancer.

Author/(Refs.)	Drug/small molecule	Mechanism	Method	Clinical stage
Vassilev *et al* (162), 2004	Nutlin-3a	Inhibits MDM2-p53 pathway	Binds to MDM2 to block the MDM2-p53 interaction	Preclinical
Issaeva *et al* (164), 2004	RITA	Inhibits MDM2-p53 pathway	Binds to p53 to block the MDM2-p53 interaction	Preclinical
Bykov *et al* (168), 2002	PRIMA-1	Restores wild-type function of p53	Restores DNA contact and convert mutant p53 conformation to wild-type	Phase I/II
Yu *et al* (165), 2012	NSC-319726	Restores wild-type function of p53	R175H mutation converted to wild-type	Preclinical
Tang *et al* (167), 2007	CP-31398	Restores wild-type function of p53	Mutant p53 core domain stabilisation	Preclinical
Li *et al* (169), 2011	HDAC6 Hsp90	Degradation of mutant p53	Interrupts HDAC-p53 interaction	Preclinical

MDM2, mouse double minute 2; RITA, reactivation of p53 and induction of tumour cell apoptosis; PRIMA-1, p53 re-activation and induction of massive apoptosis; HDAC6, histone deacetylase 6.

Another promising target for pancreatic cancer is p53-mediated therapy. MDM2, a feedback regulator of p53, is upregulated and frequently amplified in cancers, rendering the MDM2-p53 pathway the optimal target for therapy (161). Several drugs have been formulated to disrupt the p53-MDM2 pathway such as Nutlin-3a, a selective inhibitor of MDM2, designed to block the MDM2-p53 interaction, which can induce cell cycle arrest and apoptosis by blocking the G1 and G2 phases (161-163). In animal models, Nutlin-3a has been demonstrated to induce the activation of p53 signalling, as well as the suppression of tumour growth (161). Another drug, RITA, is a small molecule that activates the p53 pathway and has successfully demonstrated suppression of tumour growth in animal models (164).

Small molecules, including CP-31398, PRIMA-1 and NSC-319726, can alter mutant p53 to exhibit wild-type p53 functions. PRIMA-1 restores the DNA binding domains by converting the conformation of mutant p53 (R273H and R175H) to wild-type p53 (165,166). NSC-319726 has been tested to restore the structure and function of wild type p53 in R175H mutations, while CP-31398 stabilises the DNA binding domain of p53, increasing the transcriptional activity (165,167). By

restoring the wild-type p53 functions, it is enabled to carry out apoptosis and cell cycle arrest (168).

Lastly, the degradation of mutant p53 in PDAC using inhibitory factors, such as HDAC1 and HDAC2 inhibitors, block the HDAC signalling pathway. HDAC and p53 interaction is responsible for stabilising the mutant p53, rendering it more stable than the wild-type p53 (115,169,170). Table III summarises the p53-mediated therapeutics in pancreatic cancer.

7. Conclusion and future directions

The mortality rate of patients with pancreatic cancer continues to increase due to the lack of appropriate screening markers for early detection. As the understanding of biology surrounding the p53 family grows, their role in pathogenesis of cancer may be a target for cancer detection or therapy.

In this review, the structure of p53 family isoforms, and the role of wild-type p53, mutant p53, TAp63, DNp63, TAp73 and DNp73 were discussed. Particularly in pancreatic cancer, it is apparent that in addition to the loss of the apoptotic ability of p53, mutations in this gene leads to gain of cancer-promoting properties through various pathways, such as the inhibition of regulatory genes, promoting growth through the PDGFRβ pathway, as well as the manipulation of autophagy in cells. As for p63 and p73, the function of each isoform forms a paradox as they have contradictory properties in cancer. In actuality, the function of each isoform varies based on the origin of cancer and seems to be tissue-specific.

There is still much to learn about the exact role of p53 family isoforms in cancer. In fact, due to their functional similarity and tissue specificity, how each gene and their isoform interact with each other is particularly attractive for future research. In addition, future research should shift its focus to clinical trials for therapeutic targets such as RUNX2, Itch, MDM2 and DNp63 in order to elucidate more effective strategies for the treatment of pancreatic cancer.

Authors' contribution

CLL conceived the study; HJ and ALF acquired and analysed the information and drafted the review; CLL revised it critically for important intellectual content; all authors approved of the version to be published, and are accountable for all aspects of the work. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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